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DISTRIBUTION OF THE PATTERNS OF VENTRICULAR POTENTIAL WHICH DETERMINE THE FORMS AND SIGNIFICANCE OF ELECTROCARDIOGRAMS

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We have recently reported[2] observations concerning the distribution of potential of ventricular origin on the body surface which demonstrate that two patterns of potential variation, one of which can be recorded when an exploring electrode is placed on the anterior chest wall just to the right of the heart, and the other, just to the left of the heart, are each well preserved along a surface line to the homolateral shoulder tip. It was found, however, that decrement (*i. e.*, diminution in magnitude of potential variation) occurs as distance from the heart increases. Because of these characteristics, it was possible to demonstrate certain relationships of potential among groups of positions along each of these lines. Thus, groups of three positions can be found whose relationship is such that the ventricular potential of an intermediate position is approximately equal to the mean potential of a proximal and distal position, despite the fact that there may be considerable difference of potential between the two latter positions. Moreover, groups of three positions can be found along each of these lines whose relationships

* Now on leave of absence "on active service."

indicate either that the potential variations of the proximal position are approximately equal to the sum of the potential variations of the two distal positions from an assumed base line of zero potential at every instant of the ventricular cycle, or that each position in such groups includes the same pattern of unrecognized potential variation. The improbability of the latter alternative has been pointed out.

In our former paper we designated these two patterns which could be traced far from the precordial region (Fig. 1) either by pairing electrodes at appropriate positions along each line or by the method of balanced potentials, as the "C_1 pattern" and the "C_5 pattern,"

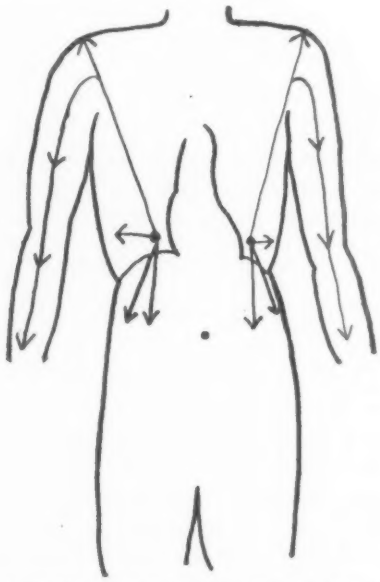

FIG. 1.—Diagram indicating by lines and arrows the directions along which distribution of the C_1 and "extra-apical" patterns of potential can be demonstrated.

using the conventional meanings attached to the C_1 to C_6 positions (across the precordium from right to left). It was pointed out that the C_1 pattern sometimes remains intact as near to the heart as the C_2 position and can be recognized as far from the heart as the right arm or tip of the right shoulder, unless decrement is so great that potential variations become quite small at the distal areas. Under such circumstances even slight technical errors which remain constant assume greater relative importance, so that they may distort the recorded pattern and mask the relationship. Moreover, it should be emphasized that minor modifications in pattern are to be expected, since these regions are not insulated from the remainder of the body. The "C_5 pattern" is usually well maintained on the

left side, so that it is easily recognizable as far away as the left arm and left shoulder. The term "C_5 pattern," however, is an unsatisfactory designation since the location of the position on the left chest wall which fulfills these relationships is not always the C_5 position. This is probably due in part to differences in anatomic relations of the left border of the heart to the chest wall. The position is usually found just outside the left border of the heart somewhere between the C_4 and C_6 positions. Occasionally, however, the pattern found over the arm and shoulder is not fully maintained as low as the level of the C positions, but is maintained to a level 1 inch or 2

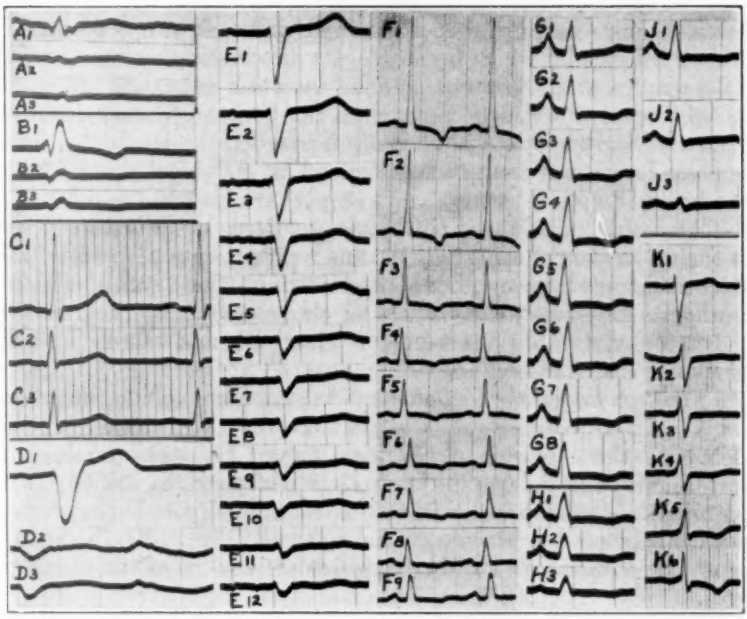

FIG. 2.—Electrocardiograms under various conditions illustrating distribution of potential. (See explanation in text, section preceding Summary.)

higher. For these reasons we have abandoned the term "C_5 pattern" for the more accurate although less convenient designation "extra-apical pattern." The similarity of the C_1 and right arm patterns, and of the extra-apical and left arm patterns was shown in the paper mentioned, but can be demonstrated in a more striking way by adjustment in sensitivity of the galvanometer so that the amplitude of the deflections recorded at the C positions is comparable with that of the arms (Fig. 2, *A*, *B*, *C* and *D*). It was shown that Lead I is formed almost entirely by the extra-apical pattern, subject to the decrement found in the left arm, minus the C_1 pattern subject to the decrement found in the right arm.

The studies which formed the basis of the previous report suggested that, aside from the patterns found on the precordium inside and exclusive of the C_1 and the extra-apical positions and adjacent areas above and below, there are but three major patterns of potential variations on the body surface which can be detected by electrocardiography. In certain areas, however, particularly about the attachment of the diaphragm, there may be sufficient overlapping in the distribution of these patterns to result in composite configuration. The three major patterns are: (1) the C_1, and (2) the extra-apical patterns mentioned above, and (3) a pattern found by the method of balanced potentials when the exploring electrode is placed anywhere on the body below the attachment of the diaphragm to the trunk, except on the abdominal wall near the precordium. This third pattern which because of its distribution we have called "the diaphragmatic pattern," unlike the other two, does not seem to be subject to rapid decrement on the body surface as distance from the heart increases, but is often found to be much the same in areas far distant from each other and at variable distances from the heart (Fig. 2, *G1–8*).

The method of balanced potentials previously described was used in the major part of this study dealing with patients. Observations were made on a large number of cases with common types of electrocardiographic abnormality such as those caused by ventricular hypertrophy, the various types of infarction, and bundle branch block.

1. *Distribution of the C_1 Pattern.* As stated above, in some cases the C_1 pattern remains intact as near the ventricles as the C_2 position. As the exploring electrode is moved to positions along a surface line from the C_1 position to the tip of the right shoulder, the pattern is well maintained as distance from the C_1 position increases, until the deflections become extremely small (Fig. 2, *E1–7*). Sometimes the pattern can still be recognized at the tip of the shoulder (Fig. 2, *E8*). The deflections obtained on the right arm are always smaller than those of the anterior axillary region and always larger than those obtained at the tip of the shoulder. Although the matter has not been fully studied, various positions on the right anterior and lateral chest wall at some distance from this line may also yield much the same pattern. If a surface line is drawn across the right side of the back from the tip of the right shoulder to the diaphragmatic level, at a point midway between the spine and the posterior axillary border, and the exploring electrode placed at various areas along this line, the results are as follows: the deflections grow smaller between the tip of the right shoulder and the spine of the scapula (Fig. 2, *E8–11*). At the latter area they are usually smaller than at any other area on the body surface. As the exploring electrode is carried down the back toward the diaphragm, larger deflections having the C_1 pattern are sometimes found but near the dia-

phragm the C_1 pattern tends to be lost. This finding will be referred to later as well as the distribution of the C_1 type of potential on the abdomen.

2. *Distribution of the Extra-apical Pattern of Potential.* The distribution of the extra-apical pattern of potential on the left chest, shoulder and arm is very similar to that of the C_1 pattern on the right side. The most convenient method that we have discovered for finding it in a position near the heart is the following: Tracings are made by the method of balanced potentials with the exploring electrode on the left arm and then on a series of 5 evenly spaced areas along the line between and including the C_4 and C_6 positions. From one or more of these positions a pattern can be obtained, which so far as our experience goes always resembles that of the left arm. Occasionally, however, as has been stated, the *closest* resemblance cannot be found at this level, but may be found 1 inch or more above the level of the apex along the line from a position just outside the apex to the tip of the left shoulder. As the exploring electrode is carried along this line to various areas nearer the shoulder, decrement may not begin to manifest itself until the electrode position is at least 2 or 3 inches above the level of the apex. Above this area decrement is rapid as distance from the heart increases, although the deflections are usually fairly large at the tip of the left shoulder (Fig. 2, *F1–6*). The extra-apical pattern is well maintained there, unless because of some pathologic condition deflections had been small at the extra-apical position and are therefore extremely small at the tip of the shoulder. With this exception the amplitude of deflections obtained with the exploring electrode on the left arm is usually considerably greater than in the case of the right arm. If a surface line is drawn from the tip of the left shoulder posteriorly to the level of the diaphragm about midway between the spine and the left posterior axillary line (similar to the line described on the right side) and the exploring electrode placed along this line, the findings are as follows: the extra-apical pattern may undergo further decrement at areas along the line to about the level of the spine of the left scapula (Fig. 2, *F6–9*). When potential variations are small at the extra-apical position, they are almost negligible over the spine of the left scapula, often being even smaller than on the right side. Below the spine of the scapula there may be little or no further decrement and the amplitude of deflections may actually increase. However, as the diaphragmatic level is approached the pattern may show considerable change, as it does on the right side.

3. *The Diaphragmatic Pattern of Potential.* The diaphragmatic pattern can be recognized in tracings made by the method of balanced potentials whenever the exploring electrode is placed on the parts of the body surface below the level of the diaphragm posteriorly, on the right flank below the diaphragm, the left flank below

the diaphragm (unless the heart extends well toward the axilla), the lower abdomen and both legs. The deflections as a rule do not vary much in amplitude in these areas, thus failing to show the marked decrement observed in the two other patterns, as distance from the heart increases (Fig. 2, *G1–8*). On the right side of the back, rapid decrement of the diaphragmatic pattern is observed as the electrode is moved to positions successively higher above the attachment of the diaphragm so that deflections decrease and the pattern may be gradually lost in the course of a few inches (Fig. 2, *H1*, *2* and *3*). On the left side, however, the extra-apical pattern is usually so well transmitted to the back above the diaphragm that a similar observation cannot be made and the attachment of the diaphragm often marks an almost abrupt transition from one pattern to the other (Fig. 2, *K1–6*). However, in certain cases with small deflections at the C_5 position, decrement is such that these latter potential variations may become negligible on the back of the chest. Under such circumstances the rapid decrement and loss of the diaphragmatic pattern of potential above the attachment of the diaphragm can be demonstrated just as it can be on the right side (Fig. 2, *J1*, *2* and *3*).

4. *Precordial Potential Patterns Between the C_1 and Extra-apical Positions and Their Distribution.* It is well known that, as an exploring electrode is moved from the C_1 position to successive C positions to the left, and tracings made at each of these areas, the pattern tends to show at least some change, so that no two are exactly alike. If a definitely pathologic pattern is recorded at one of these areas, it is also reflected at least to some extent at nearby areas. When marked differences are recorded from adjacent C positions, a series of tracings made from areas between the two shows the change to be gradual rather than abrupt (Fig. 3, *B1–5*). Special methods of pairing electrodes are not required to demonstrate these phenomena. They suggest that there is considerable overlapping of the cardiac volumes which contribute most of the potential to precordial surface areas near each other.

If, in the study of the various precordial potential patterns, the method of balanced potentials is used, or the exploring precordial electrode is paired with an electrode on an area of relatively slight potential variation such as the right scapular region,* and an arbitrarily chosen test lead is simultaneously recorded for the purpose of timing the deflections found in each position with reference to those of other precordial positions, the following facts can be demonstrated: (1) potential variation seems to begin at the same instant on every part of the precordium (Fig. 3, *A1–5*, *D1–5*,

* The patterns obtained by these methods of pairing do not differ materially from those obtained by pairing the exploring electrode with one placed on the right arm unless there is considerable difference of potential between the right arm and the right scapular position. Even in such cases the C_1 and C_2 patterns remain practically intact although the amplitude of deflections may be less in the CR leads.

Fig. 4, *A1–5*), although occasionally in certain areas there may be a close enough balance of electromotive forces that our relatively crude methods of recording may fail to show potential variation. (2) Over normal hearts, at the C_1 position there is an initial positive potential variation of relatively small magnitude, terminated by a sharp wave of negativity. As the exploring electrode is moved to the C_2, C_3, C_4, C_5 and C_6 positions successively, the positive potential tends to increase in magnitude with each shift in position as far to the left as the C_4 or C_5 position (depending upon the relation of the cardiac apex to the chest wall) but in all these positions it is terminated by a sharp change in direction of potential variation (Fig. 3, *A1–5*). These waves, as has been pointed out by Wilson

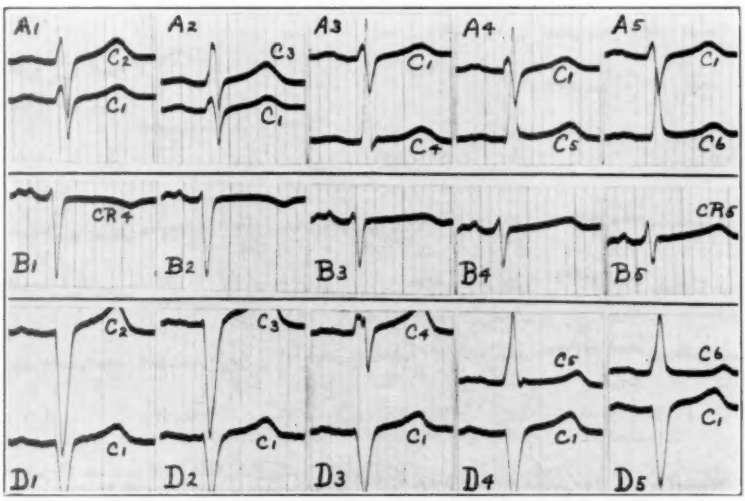

FIG. 3.—Electrocardiograms under various conditions illustrating distribution of potential. (See explanation in text, section preceding Summary.)

using a different method,[1] seem to correspond to the pre-intrinsic and intrinsic waves of epicardial electrograms. In certain cases initial negative potential of small magnitude may be found at the C_4 or C_5 position. When it is found at the C_4 position, its magnitude is usually slightly greater at the C_5 position. In such cases there is delay in the onset of positive variation at the positions where potential variation is initially negative. The T wave potential variation is normally positive at all the C positions to the left of the sternum. Thus with such methods of pairing electrodes, problems of standardization become relatively simple. (3) When notching or splintering of the QRS complex is present, suggesting that two pairs of pre-intrinsic and intrinsic-like waves are being recorded at slightly different time intervals, it can sometimes be shown that one of these

pairs shows maximum deflections at the C_1 or C_2 position and the other at the C_4, C_5 or C_6 position (Fig. 3, *D1–5*, Fig. 4, *A1–5*). This indicates that they are derived from different parts of the heart.*

We have previously shown that the C_1 and extra-apical patterns are distributed over the anterior abdominal surface although with considerable decrement as distance from the heart increases.[2] It can be shown by the same methods used to demonstrate the distribution of the C_1 and extra-apical patterns, that the patterns found at intermediate C positions are also distributed on the surface of the upper abdomen, although this relationship is somewhat obscured by the overlapping in distribution of neighboring chest patterns (Fig. 3).

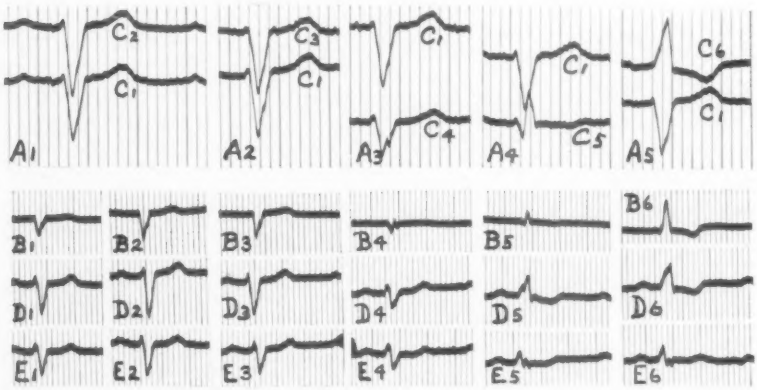

FIG. 4.—Electrocardiograms under various conditions illustrating distribution of potential. (See explanation in text, section preceding Summary.)

Studies on Experimental Animals. Observations on the rat showed that the ventricular potential of all parts of the body below the diaphragm, including the hind legs, abdominal wall, liver and intestine, is about the same (Fig. 5). This obviously means either that potential is almost uniformly distributed in this part of the rat's body, or that these tissues are almost insulated from cardiac electrical activity.

The distribution of ventricular potential was next investigated in a medium-sized dog, using needle electrodes insulated except at the tip. Nembutal anesthesia was employed. When the exploring electrode was paired with an electrode inserted beneath the skin of the right foreleg, tracings practically identical in pattern were obtained from both legs, various parts of the abdominal wall and corresponding points within the abdomen reached by puncturing through the abdominal wall (Fig. 6, *A1–8*). However, the deflections became progressively slightly larger as the exploring electrode was placed higher on the abdomen and were larger in the subcostal angle than elsewhere on the surface, indicating the presence of decrement as distance from the heart increased. From the mid-abdomen to the subcostal angle the deflections obtained by puncturing the exploring

* Observations on the contribution of each ventricle to the electrocardiogram will be presented in a subsequent paper.

electrode through the abdominal wall were slightly although appreciably larger than those obtained from the corresponding surface area.

When the abdomen was opened and the exploring electrode inserted directly on the diaphragm, practically the same pattern was recorded everywhere except near to and directly under the heart (Fig. 6, *B1–7*). This pattern was like the one recorded from the legs, the abdominal wall and within the abdomen. However, as the exploring electrode was moved from various parts of the periphery of the diaphragm to positions nearer the heart, much greater increase in amplitude of deflections was observed than had been found by moving the electrode comparable distance on the abdomen. Near to and directly under the heart, not only were the deflections larger than elsewhere but also as the electrode was moved from one

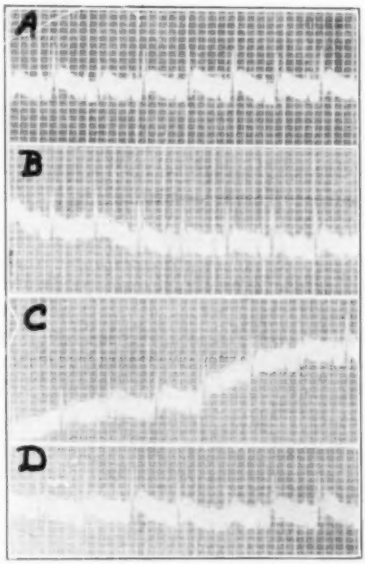

FIG. 5.—A series of electrocardiograms made in a rat. In *A* the tracing was made with electrodes paired on the left hind leg and right fore leg with the polarity as in Lead II. In *B* the left leg electrode was shifted to the abdominal wall, in *C* to the surface of the liver, and in *D* to the surface of intestinal loops. Note the similarity of pattern and size of deflections in all these tracings.

position to another, the patterns changed materially. Examination of the configuration of T waves in the patterns found near the heart suggested that the potential of the diaphragm at all positions farther from the heart was in effect a composite of these proximal patterns. It would appear, therefore, that the potential of all parts of the body below the diaphragm was derived from the same sources as the patterns found on the diaphragm. Furthermore, it would appear that: (1) decrement in potential on the diaphragm was considerable as distance from the heart increased; (2) it was proportionately less rapid although still appreciable on the upper abdomen; and (3) below the mid-abdomen further increase in distance from the heart caused practically no change in magnitude of deflections.

When the exploring electrode was inserted upward through the dome of the left diaphragm, the pattern obtained from a position just above the

diaphragm was much the same as that found on the corresponding under surface although the QRS complex deflections were larger and the T wave smaller (Fig. 6, *B6* and *C1*). As the electrode was pushed upward into the left lung and tracings were made at intervals of about 1 cm., gradual change

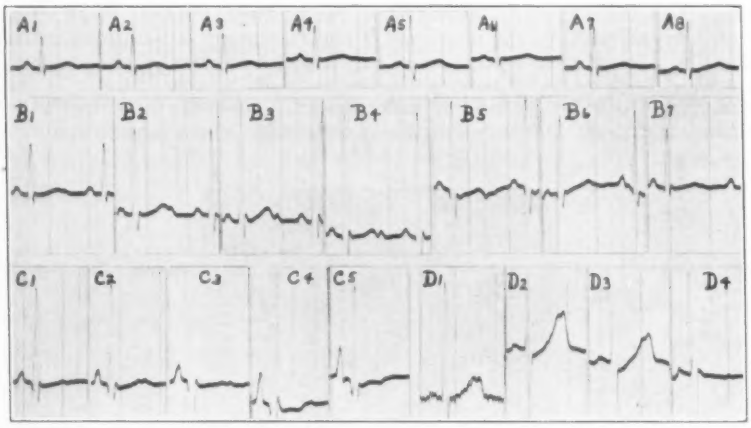

FIG. 6.—Electrocardiograms under various conditions illustrating distribution of potential in the dog. (See explanation in text, section preceding Summary.)

in pattern occurred in the lower 3 cm. of the lung (Fig. 5, *C1–5*). When the exploring electrode was pushed through the dome of the right diaphragm and the same procedure followed, the differences in pattern were

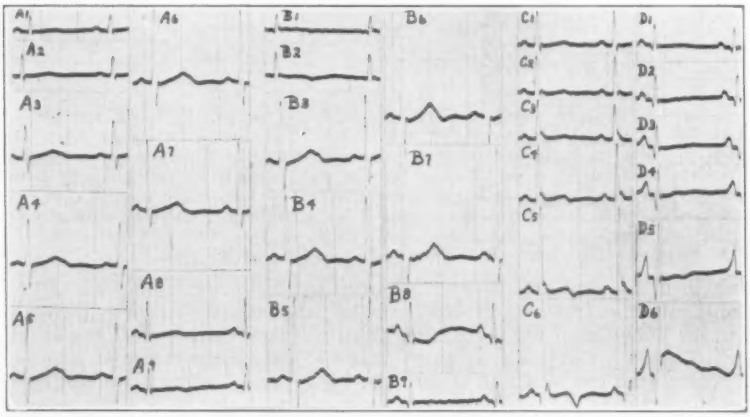

FIG. 7.—Electrocardiograms under various conditions illustrating distribution of potential in the dog. (See explanation in text, section preceding Summary.)

slightly greater than had been found on the left side (Fig. 6, *D1–4*). It is possible, however, that the electrode was nearer the heart on the right side. In this series of experiments, the exploring electrode was probably never less than 3 cm. nor more than 5 cm. distant from some part of the external

surface of the heart. It was evident that considerable potential variation develops within the substance of both lungs and that the potential of areas near to the heart and to each other may differ considerably.

Study of the patterns obtained when the exploring electrode was placed on the chest wall suggested that decrement occurred as distance from the precordium increased, in somewhat the same manner as in the human (Fig. 7, *A1–9*). However, considerable change in pattern was noted at areas distant from the heart. We have made no attempt to develop the method of balanced potentials in the dog and have therefore not ruled out the possibility that these changes in pattern are due to the relatively greater influence of the right foreleg potential variations on the configuration of electrocardiograms when the exploring electrode is placed at some distance from the precordium.

When the exploring electrode was inserted through the chest wall for a distance of 1 to 2 cm., the deflections were as a rule slightly greater than those found in the corresponding overlying subcutaneous tissues (Fig. 7, *B1–9*). However, the configuration of the patterns obtained from corresponding points inside and outside the chest wall remained much alike in most regions. The chief exception to this rule was noted in the configuration of T waves in certain axillary positions. As electrodes were inserted from the lateral walls of the chest deeper into lung structure, approaching the posterior aspect of the heart, the deflections became considerably greater (Fig. 7, *C1–6*, *D1–6*). The patterns in superficial parts of the lung, which showed resemblance to those of the outer chest wall, were considerably different from those obtained in deeper parts of the lung near the heart. Tracings made at 1 cm. distances from each other showed these changes to be gradual in occurrence.

Discussion. In the dog and the rat there appears to be distribution of one pattern of potential variation to nearly all parts of the body below the diaphragm, including the surfaces of the intra-abdominal tissues. In the dog, fairly rapid decrement can be demonstrated on the diaphragm as distance from the heart increases. Slight decrement can also be demonstrated on the upper abdominal wall. In the human, as our experiments have shown, there is a much larger area of practically uniform distribution of potential on the lower part of the body than had hitherto been thought. The human differs from the dog in that, in the former, it is possible to demonstrate that precordial patterns of potential are distributed to some extent on the surface of the upper abdomen. However, limited studies of the potential of the interior of the stomach in the human fail to reveal evidence of distribution of the precordial patterns to that region. The pattern of potential variation conforms fairly closely to the diaphragmatic pattern, but tends to be of greater magnitude than those of the legs. Thus, in the human as well as in the dog, it may be that there is widespread distribution of the diaphragmatic pattern of potential on and below the diaphragm and that in parts of the body near the heart, the phenomenon of decrement may exist in the human as it does in the dog. It is probable that the distribution of the precordial patterns of potential to the upper abdomen in the human is mainly through electrical pathways in the abdominal wall.

It was known by Einthoven that the potential variation of cardiac origin of all parts of the surface of each extremity is practically uniform and that the potential is practically identical in both legs. We have previously shown that slight differences of potential can often be recorded when electrodes are paired on the outer and inner aspects of the upper arms near their attachments to the trunk, particularly on the left side.[3] These changes, however, are not great enough to invalidate Einthoven's assumption regarding the distribution of potential in extremities, which is one of the minor supports of the equilateral triangle hypothesis. His major assumption, although he did not explicitly state it as such, is that the body tissues function as a homogeneous fluid volume conductor. If this assumption be valid, only relatively unimportant error would be introduced by his further assumptions that: (1) the heart may be considered as equidistant from the vertices of the angles of an equilateral triangle, formed by lines connecting the attachments of the arms and the pubis; and (2) the heart is far enough away from the extremities that no part has an advantage over any other part, by virtue of its position, in producing potential changes in the extremities.

On the basis of evidence now at hand, it seems safe to say that the laws governing the distribution of potential in an extensive medium of uniform conductivity are not applicable to the distribution of potential throughout the human body, probably because of differences in the electrical characteristics of the various tissue structures between the heart and the body surface. All of our findings seem to emphasize the importance of these structures even to the extent that the body can be divided into various regions, in each of which certain characteristic differences in the distribution of potential can be discovered. Thus, as has been shown, in the region closely surrounding the heart (probably not more than 2 or 3 inches from some part of its external surface) the potential variations appear to decrease very markedly as distance from the heart increases. Moreover, throughout this region, the pattern of potential variations is found to differ in positions near each other just as it does on the precordium (which is a part of the region under consideration).

The C_1, extra-apical, and diaphragmatic patterns, however, each of which has its own region of distribution, appear to dominate the potential variations of nearly all other parts of the body. These patterns, as judged from the effects produced on them by myocardial infarction, seem almost independent of each other, although complete independence would doubtless be impossible. The modes by which each of the three is directed to its own large area of body surface, where the effect of other ventricular electrical activity is practically negligible, cannot be satisfactorily explained at this time. It seems possible that the distribution of these three patterns

depends largely on areas of contiguity of the diaphragm and the lungs to the heart and the special anatomic and electrical characteristics of these structures. However, studies in patients with unilateral pneumothorax in which the lung is not in contact with the chest wall (not reported in this paper) indicate that conduction may occur *via* the precordium and lateral chest wall independently of the lungs. Thus, it seems possible that the C_1 and extra-apical patterns receive some accretion *via* the precordium as well as through the lungs. If, as seems certain, precordial and diaphragmatic potential variations depend mainly on electrical activity in limited volumes of the heart, our demonstration of the distribution of these potential patterns indicates that electrical activity in certain limited volumes of the heart dominates the potential variations of large areas of the body surface, including the extremities.*

The phenomenon of decrement observed in the upper part of the body must depend on the structure and electrical characteristics of the conducting media. In the case of extensive conductors, the magnitude of potential change may be expected to vary in some inverse relationship with distance from the source of electrical activity. The practically uniform distribution of potential through out all parts of the surface of any one of the arms or legs, irrespective of relative distances from the heart, is probably owing to the facts that: (1) the tissues of the arms and legs are good conductors; and (2) because of their structure further dispersion of electrical pathways is not possible, thus current flow throughout extremities is in effect limited to one dimension so that the extremities function electrically much as wires. The comparatively slight decrement in the diaphragmatic pattern of potential on the trunk below the diaphragm is more difficult to explain, although after this pattern has been distributed throughout the diaphragm, which probably functions as a plane conductor, the situation may be somewhat analogous to that of the extremities. The apparently limited distribution of the diaphragmatic pattern above the diaphragm is a perplexing phenomenon and raises the question as to what part the lungs play in obstructing the upward distribution of this pattern. That it is well distributed just above the diaphragm is clearly shown when the exploring electrode is punctured through the diaphragm of the dog.

The demonstration, by the use of the method of balanced potentials, of hitherto unsuspected facts regarding the distribution of potential suggests that certain changes in the methods of electrocardiography may be desirable. One of the first questions we must ask ourselves is, whether the preoccupation with limb leads is justifiable. If the equilateral triangle hypothesis cannot be upheld,

* We do not imply by these statements that electrical activity in any part of the heart fails to influence the potential of any part of the body. We are concerned here with those effects which dominate the pattern.

limb leads must justify themselves entirely on empirical grounds. The following statements may be made in defense of them: (1) limbs are convenient positions for the application of electrodes, (2) countless limb lead electrocardiograms have been made, (3) limb leads have proven themselves satisfactory for the study of abnormal cardiac mechanisms, and (4) limb leads may demonstrate abnormality on the posterior wall of the left ventricle, whereas chest leads usually fail to do so.

We have already described how Lead I is formed.[2] Lead II is formed by the diaphragmatic pattern of potential, minus the C_1 pattern after each has undergone the decrement found in the positions to which the electrodes are attached. Lead III is formed by the diaphragmatic type of potential, minus the extra-apical pattern after each has undergone decrement. The measurements of the differences between pairs of these three types of potential variation, each of which is derived mainly from separate parts of the heart and each of which is greatly modified, depending on the characteristics of the electrical pathways between the heart and the limbs, have led to endless difficulties in standardization, questions as to the meaning of the direction and amplitude of various deflections, of slurrings and notchings. It would seem to us far more desirable to measure the potential of each of these areas against a constant potential if this were possible. The method of balanced potentials has already been shown, by experimental check, to be a step in the direction of this objective, but it is too time-consuming for routine clinical electrocardiography. However, as we have shown, the right scapular region is an area where ventricular potential is most often nearly the same as that of balanced potentials. Consequently the results obtained by pairing an electrode on this area with the exploring electrode are in most cases almost identical with those obtained by the method of balanced potentials. Even in cases with marked potential variations on the body surface, such as may be found in ventricular hypertrophy, the differences are not likely to be great. It seems to us, therefore, that a closer approximation to the potential of the exploring electrode can be recorded by this procedure than by any other simple method.

After fairly extensive clinical study we are convinced that a series of leads made with the exploring electrode on positions C_1 to C_6 inclusive and on either the right or left leg, paired with an electrode on the right scapular region, reflects more information of clinical value than can be obtained by conventional methods of pairing electrodes. In our opinion all three limb leads could be discarded without sacrificing any real values, and with the very great advantage of ridding ourselves, once and for all, of the infinite variability of pattern found in these leads. Much of this variability is dependent on the electrical characteristics of tissues outside the heart, so that it is of dubious clinical significance.

The matter may be illustrated by discussion of "posterior" infarction. This is the location of injury which, above all others, has justified the use of limb leads because of the changes produced in Leads II and III. However, these changes are nearly all owing to change in the diaphragmatic pattern of potential. Lead II is more dependable than Lead III for the diagnosis of posterior infarction, because potential variation in the right arm is usually considerably less than in the left arm, so that the changes in the diaphragmatic pattern are less obscured in Lead II. The superiority of a lead in which an electrode is placed over the right scapula instead of the right arm is owing to the fact that potential variations are even less on the scapula than on the arm, so that a closer approximation to the really significant changes in the diaphragmatic pattern is obtained.

In view of the inadequacy, suggested by this study, of the generally accepted methods of making electrocardiograms, one may ask how methods which seem to be so imperfect and to include so much irrelevancy have enabled electrocardiography to maintain its important position in cardiac diagnosis. So long as limb leads only were being made, electrocardiography owed much of its standing to the fact that it was almost always a satisfactory procedure for the display of abnormalities of cardiac mechanism. That it had obvious limitations as a diagnostic procedure for the discovery of injury of the myocardium was not difficult to demonstrate. That these limitations were not even greater is because (1) the potential variations of ventricular origin on the right arm are as a rule comparatively small in magnitude, and (2) they are relatively little affected by involvement of the left ventricle. Thus, Leads I and II usually bear some resemblance to the extra-apical and diaphragmatic patterns of potential variation respectively, whether these be normal or abnormal in contour. Since the introduction of chest leads, the latter have been generally regarded as a useful supplement to the supposedly fundamentally important limb leads, based on the fact that in certain cases the chest leads alone reflect evidence of myocardial injury. Even the potential variations of the most inappropriate positions that can be chosen for the electrode paired with the exploring chest electrodes are as a rule unable to obscure the value of chest leads, because of the fact that potential variations at positions so near the heart as the anterior chest wall tend to be much greater in magnitude than those of positions farther from the heart. It is evident that not all of the various methods heretofore proposed for pairing with the exploring chest electrode could yield the most significant tracings obtainable and there is no clear evidence that any of them achieve this goal. On the basis of the data presented in this paper it appears possible to devise simple electrocardiographic methods which may clarify the significance of recorded deflections and facilitate the satisfactory standardization of electrocardiographic leads.

Explanation of Figures 2, 3, 4, 6, and 7. FIGURE 2. Series *A* and *B* were obtained from a patient with right bundle branch block, the method of balanced potentials being used. *A1* represents the potential variations of the C_5 position and *A2* the potential variations of the left arm. *A3* was made in the same way as *A1* except that the sensitivity of the galvanometer was reduced so that the deflections would be comparable with those obtained when the exploring electrode was on the left arm. *B1* was made with the exploring electrode on the C_1 position and *B2* with the exploring electrode on the right arm. *B3* was made in the same way as *B1* except for reduction in the sensitivity of the galvanometer.

In series *C* and *D* the exploring electrode was paired with an electrode placed over the spine of the right scapula. *C1* represents the potential variations of the C_5 chest position. *C2* represents the potential variations of the left arm. *C3* (recorded simultaneously with *C2*) was made in the same way as *C1* (with the exploring electrode on the C_5 chest position) except that the sensitivity of the galvanometer was reduced. *D1* represents the potential variations of the C_1 chest position in a patient with left bundle branch block. *D2* represents the potential variations of the right arm. *D3* recorded simultaneously with *D2* was made in the same way as *D1* except that the sensitivity of the galvanometer was reduced. The second beat in *D2* and *D3* is a ventricular extrasystole. These illustrations are presented to show the resemblance between the C_1 and right arm patterns and the C_5 and left arm patterns of ventricular potential variations, when the differences due to decrement as distance from the heart increases are neutralized by appropriate adjustment in the sensitivity of the galvanometer.

Series *E* represents electrocardiograms made by the method of balanced potentials with the exploring electrode on various positions of the right upper part of the body. *E1* represents the potential variations of the C_1 position. *E6* was obtained with the exploring electrode on the right anterior axillary fold. *E2–5* were obtained from positions 1 to 1½ inches further from the C_1 position respectively along the line between the C_1 position and the right anterior axillary fold. *E7* represents the potential variations of the right arm and *E8* those of the tip of the right shoulder, *E9* and *E10* were made with the exploring electrode in positions along the line between the tip of the right shoulder and the spine of the right scapula. In *E11* the exploring electrode was over the spine of the right scapula and in *E12* it was placed below that position. This series of tracings illustrates the similarity of ventricular potential variations over a large part of the right thorax, shoulder and arm. Decrement as distance from the heart increases is demonstrated.

Series *F* represents electrocardiograms made by the method of balanced potentials in a patient with left ventricular hypertrophy, the exploring electrode having been placed on various positions of the left upper part of the body. *F1* was made along a line between a surface point just outside the cardiac apex and the tip of the left shoulder, the exploring electrode having been placed at a level 1½ inches above the cardiac apex. The tracing made from a position just outside the apex was practically identical with *F1*, there being no appreciable decrement. *F4* represents the potential variations of the left anterior axillary fold and *F2* and *F3* those of intermediate positions between *F1* and *F4*. *F5* represents the potential variations of the left arm and *F6* those of the tip of the left shoulder. *F9* represents the potential variations over the spine of the left scapula; *F7* and *F8* those of intermediate positions between the tip of the left shoulder and the spine of the left scapula. This series illustrates the similarity of ventricular potential variations over a large part of the left side of the thorax, shoulder and arm. Decrement as distance from the heart increases is demonstrated.

Series *G* (same patient as in series *E*) made by the method of balanced potentials with the exploring electrode on various positions below the umbilicus. In *G1* the exploring electrode was on the left leg, in *G2*, on the right flank, in *G3* below the C_1 position, in *G4* below the C_2 position, in *G5* below the C_3 position, in *G6* on the left flank, in *G7* on the left lower back and in *G8* on the right lower back.

This series is marked by uniformity of the patterns with only very slight decrement as distance from the heart increases.

Series *H* (same patient as series *E*) made by the method of balanced potentials. *H1* was made with the exploring electrode on the right side of the back at the level of the diaphragm. Note the similarity of pattern to the *G* series. *H2* and *H3* were made along a vertical line erected from the *H1* position, at 2-inch intervals. Note the rapid decrement above the diaphragm. Continuance of exploration upward (not shown here) reveals change to the pattern shown in *E12*, *i. e.*, from the diaphragmatic to the C_1 pattern.

Series J (same patient as in series *E*) made by the method of balanced potentials. *J1* was made with the exploring electrode on the left side of the back at the level of the diaphragm. Note the similarity of pattern to the *G* series and that of *H1*. *J2* and *J3* were made at 2-inch intervals along the vertical line erected from the *J1* position. Note the rapid decrement above the diaphragm. This demonstration can be made because potential variation at the C_5 position was slight and there was consequently insignificant potential variation of the C_5 type on the left side of the back.

The *K* series (made by pairing the exploring electrode with one placed over the spine of the right scapula) is designed to illustrate the abrupt change in pattern of potential variation on the left side of the back at about the level of the diaphragm due to the distribution of both the diaphragmatic and extra-apical patterns of potential into this area. In *K1* the exploring electrode was placed on the left leg. In *K2* it was placed on the left side of the back 4 inches below the level of the attachment of the left diaphragm. *K3* was made from a position $1\frac{1}{2}$ inches higher, *K4* from a position just below the diaphragm, *K5* from a position just above the diaphragm, and *K6* with the exploring electrode on the C_6 position. As the exploring electrode is moved upward the increasing influence of the extra-apical pattern is readily discerned.

(Camera speed in the *F* and *K* series was 41 mm. per second. In all others it was 75 mm. per second.)

FIGURE 3. In the *A* series the exploring electrode (whose location on the chest at various C positions is designated) was paired with an electrode on the right scapula. The QRS complex begins at approximately the same instant in all tracings. The upward deflection increases in amplitude with each change in position toward the left as far as the C_4 position. Frequently in the case of normal hearts it continues to increase to the C_5 position. At positions C_4, C_5 and C_6 an initial small downward deflection is often present as in this case and is normal with this method of pairing or when the method of balanced potentials is used. When the initial downward deflection is present there is delay in the onset of the upward deflection. The major deflections at C_5 and C_6 positions become progressively smaller than those obtained from the C_4 position in this case, because the heart was rather small so that decrement begins to manifest itself as distance from the heart increases.

In the *B* series, *B1* is the CR_4 lead obtained from a patient with old myocardial infarction and *B5* is the CR_5 lead. *B2*, *B3* and *B4* are tracings obtained from three intermediate positions successively farther to the left. Note the gradual transition from the CR_4 to the CR_5 pattern.

The *D* series is made by pairing the exploring electrode with one on the

right scapula as in the *A* series. The small upward and deep downward deflections noted at the C_1, C_2 and C_3 positions are completely lost at C_4 and replaced by a small rounded upward deflection. The notching is caused by a second pair of upward and downward deflections whose time incidence falls considerably later. These latter waves become much more prominent at the C_5 and C_6 positions.

FIGURE 4. The tracings were all obtained from a patient with an intraventricular conduction defect.

In the *A* series the exploring chest electrode was paired with an electrode on the right scapula. In each instance the position of the exploring chest electrode is indicated by the appropriate C designation. The QRS complex begins at approximately the same instant in each position. In the tracing made at the C_4 position there is definite notching. The first pair of upward and downward deflections corresponds in time to those found at the C_1, C_2 and C_3 positions. The second pair is represented at positions further to the right on the chest as slight slurring on the upstroke of the terminal major upward deflection. In positions further to the left, however, this second pair of deflections becomes larger. (Film speed 75 mm. per second.)

The *B* series was obtained by pairing electrodes on the abdomen, the left arm electrode being placed on a vertical line below a C position and the right arm electrode placed on a continuation of this vertical line just below the umbilicus. In *B1* the vertical line was extended from the C_1 position, in *B2* from the C_2 position, etc. Note the similarity of ventricular patterns, except for size of deflections, in *B1*, *B2*, *B3* and *B6* to those obtained when the exploring electrode was on the C_1, C_2, C_3 and C_6 chest positions respectively. The *B3*, *B4*, *B5* and *B6* patterns show evidence of being influenced not only by the *C* pattern directly above each but by adjacent *C* patterns as well. These effects are seen most clearly in *B3* which shows the notch found in the QRS complex of the C_4 tracing, and in *B6* which shows some of the early downward deflection found in the *QRS* complex of the C_5 tracing. (Film speed 41 mm. per second.)

The *D* series was made by pairing an exploring electrode on the upper abdomen with an electrode on the right scapula. In each instance the D position was directly below the corresponding C chest position and just below the costal margin. The similarity of pattern in each instance to that of the C position just above is obvious.

In the *E* series the exploring electrode was placed 2 inches below the corresponding D position. Decrement is quite obvious although in *E5* and *E6* considerable change in pattern occurs so that there is no longer any resemblance to the C_5 and C_6 patterns. (Film speed 41 mm. per second.)

FIGURE 6. All tracings made on one dog. (Film speed 75 mm. per second.) The exploring electrode in each instance was paired with an electrode inserted into the subcutaneous tissues of the right foreleg. The polarity is such that an upward deflection represents relative positivity of the exploring electrode.

In the *A* series the positions of the exploring electrode were as follows: *A1* subcutaneous tissue of right leg, *A2* left leg, *A3* lower abdomen, *A4* upper abdomen, *A5* high as possible in the subcostal angle, *A6* within lower part of the abdominal cavity, *A7* within upper part of the abdominal cavity, *A8* within abdominal cavity high as possible in subcostal angle. Note the similarity in pattern of all these tracings and the fact that those obtained from the subcostal angle and from within the upper abdomen show larger deflections than those obtained when the exploring electrode was farther from the heart.

In the *B* series the abdomen was open and the exploring electrode placed on the undersurface of the diaphragm. In *B1* it was placed on the right lateral margin, in *B2*, 1 inch toward the midline, in *B3* just to the right of the

midline, in *B4* directly under the heart, in *B5* just to the left of the heart, in *B6* 1 inch from the left lateral margin, in *B7* on the left lateral margin. Note the similarity of patterns in *B1*, *B2*, *B6* and *B7* to the *A* series (except for absence of the small initial downward deflection in positions on the right side of the diaphragm), the differences in T waves in positions near the heart and the increase in size of QRS deflections as the heart is approached.

In the *C* series the exploring electrode was punctured through the dome of the left diaphragm. In *C1* it was placed just above the diaphragm and in *C2*, *C3*, *C4* and *C5* it was moved successively 1 cm. higher into the lung substance. Note the general resemblance of the *QRS* complex in *C1* and *C2* to those of *B5*, *B6* and *B7*. The T waves in *C1* and *C2* are not very different from those of *B6* and *B7* although the pattern changes as the electrode is inserted further into the lung substance.

In the *D* series, the exploring electrode was punctured through the dome of the right diaphragm. In *D1* the electrode was placed just above the diaphragm and in *D2*, *D3* and *D4* it was moved successively 1 cm. higher into the lung substance. The QRS complex in *D1* is very similar to that of *B1*, *B2* and *B3* (except for absence of the small terminal upward deflection in *D1*), although the T wave is comparatively greater in amplitude. Note the changes in pattern as the electrode is inserted higher into the lung substance.

FIGURE 7. All tracings made on the same dog as in Figure 5. (Film speed, polarity and position of the electrode paired with the exploring electrode are all the same as in Figure 5.)

In the *A* series all tracings were made with the exploring electrode placed along a horizontal line on the thorax at the level of the heart. In *A1* the exploring electrode was placed far to the right of the precordium at the right posterior axillary line. The anterior midline was approached in successive steps in *A2*, *A3* and *A4*. *A5* was made with the exploring electrode on the midline and *A6* directly over the body of the heart. *A7*, *A8* and *A9* positions were successively further to the left, the last being along the left posterior axillary line. Note the close similarity of pattern in positions *A3* to *A7* inclusive and the fact that the more nearly the exploring electrode was placed to the heart, the larger the deflections. The dog seems to differ from the human in that normally it does not tend to show a constantly changing pattern of potential variations in the precordial region, although decrement is conspicuous as distance from the heart increases.

In the *B* series the exploring electrode was punctured through the chest wall at positions corresponding to those of the *A* series. There is marked similarity in the QRS complex in each *B* tracing to the QRS complex of the overlying *A* position, except that in the case of positions comparatively near the heart (*B3* to *B7* inclusive) the deflections obtained just inside the chest wall are considerably larger than those obtained just outside. The reasons for the differences in T waves in *A2* and *B2* and *A8* and *B8* positions are not clear.

The *C* series. In *C1* the exploring electrode was inserted into the subcutaneous tissue of the right lateral wall of the chest slightly anterior to the position in *A2*. In *C2* the electrode was punctured into the right lung in the direction of the heart for a distance of approximately 2 cm. In *C3*, *C4*, *C5* and *C6* the electrode was moved successively 1 cm. in the direction of the heart. Note the gradual change in pattern and increase in size of deflections as the heart is approached.

The *D* series. In *D1* the exploring electrode was inserted into the subcutaneous tissue of the left postero-lateral wall of the chest, slightly posterior to the position in *B2*. In *D2*, *D3*, *D4*, *D5* and *D6* the electrode was punctured through the chest wall into the left lung and moved successively nearer the heart as in the *C* series. Note the changes in pattern and increase in size of deflections as the heart is approached.

Summary. 1. Patterns of potential variation found in regions not more than 2 or 3 inches from some part of the external surface of the heart differ from each other appreciably at positions no more than 1 cm. from one another. Furthermore, in these regions the magnitude of potential variations decreases rapidly as distance from the heart increases.

2. The pattern of potential variation found at the C_1 position can be demonstrated in various directions on the body surface to the right of the C_1 position with decrement as distance from the heart increases. On an area as far from the heart as that overlying the spine of the right scapula, decrement is so great that the potential variations are usually of negligible magnitude. When an electrode placed on this area is paired with an exploring electrode, the results are usually not significantly different from those obtained by the use of the method of balanced potentials.

3. The pattern of potential variation found on the surface of the chest slightly to the left of the cardiac apex (somewhere between the C_4 and C_6 positions, depending on the relation of the apex to the chest wall) can be demonstrated in various directions on the surface to the left of that position, with decrement as distance from the heart increases.

4. Not only do we know that the C_1 and extra-apical patterns are distributed on the surface of the anterior abdominal wall with very rapid decrement as distance from the heart increases, but evidence is here reported that the patterns found on the precordium between these two positions are also distributed on the anterior abdominal wall with rapid decrement as distance from the heart increases.

5. Aside from the precordial patterns mentioned above, the only other that we have found distributed on the body surface is one which we have called "the diaphragmatic pattern." The distribution of this pattern above the diaphragm with rapid decrement as distance upward increases can be demonstrated on the back. It may also be distributed above the diaphragm anteriorly but we have not been able to demonstrate it here, probably because of the magnitude of the precordial potentials in such regions. It seems to be distributed everywhere below the diaphragm with but little decrement on the body surface as distance from the heart increases. It can also be demonstrated in the lower part of the esophagus and the stomach, although in these areas the potential variations are greater in magnitude than on the surface.

6. Studies on experimental animals indicate that the diaphragmatic pattern of potential can be found everywhere below the diaphragm and on all parts of the under and upper surfaces of the diaphragm except in areas very near the heart. Decrement on the diaphragm and within the upper part of the abdomen as distance from the heart increases is demonstrable.

7. The distribution of the various potential patterns which seem to be directed to certain areas and partially insulated from other areas must depend on the special electrical characteristics and anatomic structure of the various tissues by which contact with the heart is maintained and through which electrical pathways to the body surfaces function.

8. If, as our studies seem to indicate, the patterns of potential variation found on limbs are each derived mainly from separate parts of the heart, and are subject to modification depending on the electrical and anatomic characteristics of the tissues which form the electrical pathways between the epicardium and the extremities, limb leads do not merit the scientific standing that they have been supposed to possess, and there seems to be little reason to continue making them.

Conclusion. Much of the confusion which now exists in clinical electrocardiography could be eliminated if in all leads one of the paired electrodes were attached to an area of relatively slight potential variation such as the right scapular region. Under such circumstances an electrocardiogram may be obtained which presents a relatively undistorted record of the potential variations of the exploring electrode. From data now available it is possible to say that the exploring electrode should be placed on a number of chest positions such as C_1 to C_6 inclusive, if one wishes to acquaint himself with the chief features of the various patterns which may be formed on the surface of the chest, including the two widely distributed to the upper parts of the trunk and arms. In order to obtain information regarding the pattern widely distributed below the diaphragm, it is necessary to place the exploring electrode on some position at least a few inches below the parietal attachments of the diaphragm. The best position or set of positions for this purpose has not as yet been determined.

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TREATMENT OF LEG ULCERS WITH BLOOD AND CONCENTRATED PLASMA

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Leg ulcers in patients with peripheral vascular disease are notoriously difficult to heal, and in some cases incurable. Many methods

and drugs are used in the treatment of such ulcers. These include sulfonamides locally, various antiseptics, stimulants (such as cod-liver oil ointments), gelatin boots, mecholyl iontophoresis, and so on.

Since ischemic ulcers could not be supplied with sufficient blood through occluded arteries, the idea suggested itself of withdrawing blood from the patient's antecubital vein and applying it directly to the surface of the ulcer. The method adopted, in October 1941, consisted simply in dropping or spraying the blood on the ulcer and allowing it to clot. With this simple method, obtaining the curative agent from the patient himself, ischemic ulcers were healed which had failed to heal by other methods. Then the same method was applied to varicose ulcers and these healed even more rapidly, a number after only one application of blood. Relief of pain and subsidence of reaction in the tissue around the ulcer followed the first or second application in most patients.

When it was found that blood could heal chronic ulcers, concentrated plasma made from dried plasma was tried. This supplied 8 times the quantity of constituents of an equal volume of whole blood, with the exception of red and white cells. The concentrated plasma has proved to be more effective than whole blood.

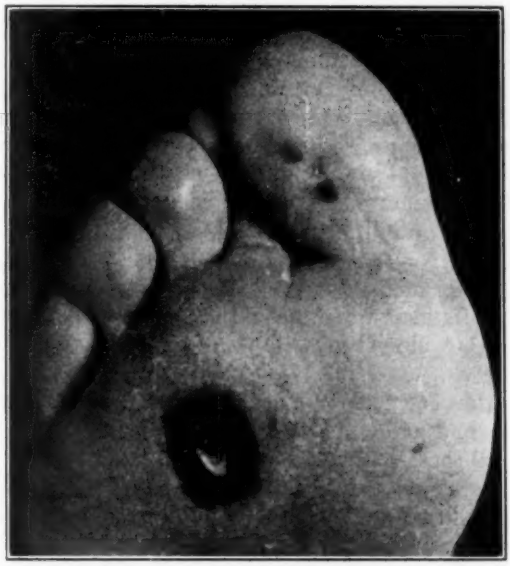
Method. The ulcer is cleaned gently with hydrogen peroxide and mopped with sterile gauze. One to 5 cc. of blood are drawn into a sterile syringe from the patient's antecubital vein. The blood is then applied to the surface of the ulcer simply by placing a number of drops on it sufficient to cover the lesion. The drops of blood may be smeared or spread over the surface of the ulcer so that a film of blood of any desired thickness may be obtained. One cc. of blood will cover an area of approximately 30 sq. cm. or 5 sq. in., so that only a small quantity of blood is required. The blood is then permitted to clot. The patient holds his leg in a position which prevents the blood from running off the ulcer. The clotting time is shortened considerably by having air blown on it by a fan. The clotting (solid) time in still air has ranged from ½ to 2 hours. A fan shortens this time to 15 minutes to 1 hour. After the blood has clotted solidly a sterile, dry dressing is applied to the treated ulcer. The lesion is reëxamined within 1 to 3 days and if the clot has been broken up or liquefied the entire procedure is repeated. For complete healing to take place, 1 to 20 applications of blood may be necessary. The larger the lesion the greater the number of applications. Most of the patients were ambulatory but patients are asked to rest as much as possible during the course of treatment.

A modification of the method was used on some patients with large lesions. Five cc. of the patient's blood were placed in an ordinary sterile nose and throat atomizer. The surface of the ulcer was then sprayed with the blood and the blood allowed to clot in the manner described above.

To treat ulcers with concentrated plasma we have used dried plasma,* diluted with only one-quarter the amount of distilled water which would ordinarily be used to restore it to the normal concentration of human plasma. In this manner the plasma contained 8 times the clotting elements and all other substances, minus red and white cells, present in an equal volume of whole blood. The concentrated plasma is then applied to the ulcer in exactly the same manner as is whole blood. The plasma is quickly clotted

* Lyovac, Normal Human Plasma, Sharpe & Dohme.

by fanning or more slowly clotted without the use of a fan. Although the plasma contains sodium citrate this does not prevent it from clotting on the surface of an ulcer. The sterile ampoule vial of concentrated plasma can then be eft in a refrigerator and used as needed.



A

B

FIG. 1.—Ischemic ulcer in a patient with diabetes mellitus. Duration of ulcer 13 months. *A*, Before treatment; *B*, 8 weeks later. Completely healed after 17 applications of patient's blood.

Results. Fifteen patients with leg ulcers have been treated with the local application of blood by the methods described above. Ten of the ulcers were on an ischemic basis, caused by arteriosclerosis and thromboangiitis obliterans; 5 were varicose ulcers. The duration of the ulcers was from 1 month to $3\frac{1}{2}$ years. All of them had been treated by various methods without healing or improving. The ulcers varied in size from 1 to 7 cm. in diameter. Nine of the 10 patients with ischemic ulcers had extreme grades of arterial occlusive disease, having either popliteal or femoral thrombosis with little or no capacity for vasodilatation. One to 20 applications were required to heal the ulcers.

Five of the ischemic ulcers were healed with blood; 1 is almost completely closed and 4 failed to heal.

Four of the 5 varicose ulcers were healed. The fifth varicose ulcer is almost healed.

Eight of the 9 ulcers which healed have remained healed for 1 to 18 months. One ulcer broke down after having been healed for 4 months.

The crust that formed on a healed ulcer gradually fell off after epithelization had taken place under it. Pain was a prominent symptom in all these patients and its rapid relief by 1 or 2 applications of blood was a striking feature of the treatment. Even those ulcers which could not be healed were painless or less painful during the course of therapy. All the patients were eager to return for further applications of blood until the ulcer healed or until we decided that the ulcer could not be healed by this method.

Another result of the treatment was the rapid reduction of the inflammatory reaction in the skin surrounding the varicose ulcers. An angry, purplish looking skin would begin to look more healthy following the first or second application of blood. The ulcers themselves rapidly became red, normal granulating tissue replacing grayish, sloughing surfaces. Three patients on whom we applied concentrated plasma had received previous treatment with whole blood. These patients improved more rapidly with the plasma than with the whole blood.

We have found the method to be harmless. Accumulation of pus occurred under a crust in 2 patients. This was readily drained by lifting off the crust after softening it with petrolatum for 24 hours. The presence of pus under a crust should be suspected if pain is not relieved.

A blood Wassermann test was done in 10 patients and found to be negative. Concentrated plasma instead of the patient's blood can be used in those with a positive blood Wassermann.

Discussion. Although we were able with blood to relieve pain quickly, reduce the inflammatory reaction and heal 9 of 15 chronic ulcers that had resisted previous methods of treatment, the mechanism of action is unknown. We know of no way of telling whether the

ulcers heal because required elements of nutrition are being supplied or because the ulcers are sealed mechanically, which permits healing to take place under the crust. The rapid relief of pain, with blood, which did not occur when other local treatment was used, suggests that the blood functioned as more than a mere mechanical seal. An interesting observation was made when concentrated plasma was used. Within 5 minutes after the plasma is applied the surface of the ulcer can be seen to change from a dull grayish pink to a bright red color, indicative of increased blood flow, at least temporarily. Perhaps the concentrated plasma with a high osmotic pressure causes capillary dilatation and increased blood flow at the surface of the ulcer.

Various substances such as dyes and tannic acid have been used to produce a crust or eschar on lesions, chiefly on burns. Blood and plasma have never been used for local medication as far as I know. This method may prove of value in the delayed healing of other wounds in which impoverished nutrition may play a part.

Summary. A simple method has been described for the treatment of ischemic and varicose leg ulcers with the patient's own blood and with concentrated plasma. Nine of 15 ulcers, refractory to other treatment, were healed, 2 were improved and 4 failed to heal. This treatment results in rapid relief of pain and subsidence of the local inflammatory reaction.

A STUDY OF THE SPLENIC VENOUS BLOOD

WITH PARTICULAR REFERENCE TO THE HEMATOCRIT PERCENTAGE AND THE HEMOGLOBIN CONCENTRATION OF THE ERYTHROCYTES, BEFORE AND AFTER SPLENIC ARTERIAL INJECTION OF ADRENALIN*

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OUR interest in the blood of the splenic vein was aroused after we had repeatedly observed the effect of subcutaneous adrenalin in producing outspoken increases in the number of circulating erythrocytes.[20] These increases were usually associated with an obvious shrinking of the enlarged spleen. Many similar observations are recorded in the literature but relatively little has been written

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about the red blood cells coming from the spleen under these conditions. A complete review of the subject of splenic arteriovenous differences up to 1933 may be found in Lauda's excellent monograph on the physiology of the spleen.[12] The evidence collected by Lauda indicated that splenic contraction was an important factor in the transient erythrocytosis produced by adrenalin. The collected evidence also indicated that the erythrocytes in the splenic vein are less resistant to hypotonic saline than those in the artery, although Lauda himself was unable to obtain decisive data on this point. Subsequent studies by Heilmeyer[10] and by Bergenheim and Fåhreus[3] support the belief that the splenic vein erythrocytes are more spheroidal.

Our primary purpose in the present study was to determine the concentration of erythrocytes in the splenic vein before and after administration of adrenalin; since if the marked increases in circulating erythrocytes were due to contraction of the spleen and emptying of the splenic reservoir, then it was to be expected that the splenic vein blood would exhibit outspoken increases in hematocrit percentage and erythrocyte count.

Method. Studies have been carried out at the time of splenectomy in 9 cases. In each instance oxalated samples of blood were obtained from the splenic artery and vein, after which 4 to 6 minims of a 1:1000 adrenalin solution were injected into the splenic artery. Two to 6 minutes later samples of blood were again obtained, in each instance from the splenic vein, and in some instances from the artery as well. Insofar as possible, these samples were taken at the time of maximum splenic contraction, whenever this was observed. It may be noted that splenic contraction was often marked, especially in the larger spleens, while it was negligible in the cases of thrombocytopenic purpura. The contraction was at times of sufficient magnitude to enhance the delivery of a large spleen through the wound.

It is quite possible that more information might have been gained had it been feasible to obtain fractional blood samples from the splenic vein from the time of injection of adrenalin until well after its effect had passed. Cruikshank,[5] for example, has reported that after section of the nerves to the cat's spleen, the first cubic centimeter of blood obtained from the splenic vein showed no change in red cell concentration while the 2d, 3d, and 4th cc., obtained individually, were increasingly concentrated, the 3d and 4th cc. exhibiting increases of 50% to 100% over the first. Although we have not obtained fractional samples in the present studies, we believe that much of the data obtained and shown in the accompanying tables are of decisive significance. The expected increase in hematocrit percentage and erythrocyte count in the splenic vein after adrenalin was noted in the majority of cases. Unexpectedly, the hemoglobin concentration of the red cells of these samples was commonly reduced, in some instances to a marked degree. (See Tables 1 to 9.)

In each instance the hemoglobin content of the blood samples was determined by means of the Evelyn photoelectric colorimeter.[8] The hematocrit percentage (corrected for the oxalate), the mean corpuscular volume, the mean corpuscular hemoglobin, and the mean corpuscular hemoglobin concentration were determined by Wintrobe's method.[21] Resistance to hypotonic saline was determined by Meulengracht's method.[16]

Results

TABLE 1.—CASE 1. FAMILIAL HEMOLYTIC JAUNDICE, W. G., ♂, 44.

Source of blood	Hgb. in gm. per 100 cc.	Hematocrit %	RBC in mill.per c.mm.	MCV in cu.μ	MCH in mμg.	MCC in %	Fragility H_1	Fragility H_2
Splenic vein	12.0	36.4	3.80	95.8	31.6	33.9	0.68	0.50
Splenic artery	12.2	37.9	3.92	97.0	31.2	32.2	0.66	0.48
Splenic vein after adrenalin	14.0	53.1	5.46	97.5	25.8	26.5	0.70	0.62
Splenic artery after adrenalin	12.9	36.1	3.97	91.0	32.5	35.7	0.68	0.52

Spleen weight 1830 gm.

Microscopic: Marked pulp congestion with narrow sinuses.

TABLE 2.—CASE 2. FAMILIAL HEMOLYTIC JAUNDICE, A. S., ♂, 41.

Source of blood	Hgb. in gm. per 100 cc.	Hematocrit %	RBC in mill.per c.mm.	MCV in cu.μ	MCH in mμg.	MCC in %	Fragility H_1	Fragility H_2
Splenic vein	15.0	41.01*	4.26	96.2	35.0	36.6	0.62	0.46
Splenic artery	15.2	49.96*	5.00	99.5	30.4	30.6		
Splenic vein after adrenalin	17.5	61.20	6.40	95.5	27.3	28.6	0.68	0.54
Splenic artery after adrenalin	15.8	40.60	4.20	96.7	37.6	38.9	0.66	0.48

Spleen weight 675 gm.

Microscopic: Marked pulp congestion; sinuses prominent and open.

* This isolated discrepancy is unexplained except as an inadvertent exchange of the data for vein and artery, in which event the hematocrit percentage of 49.96 would be readily explained as due to a spontaneous partial emptying of the splenic reservoir.[20]

TABLE 3.—CASE 3. FAMILIAL HEMOLYTIC JAUNDICE, J. B., ♀, 10.

Source of blood	Hgb. in gm. per 100 cc.	Hematocrit %	RBC in mill.per c.mm.	MCV in cu.μ	MCH in mμg.	MCC in %
Splenic artery	13.65	39.3	4.33	91.0	32.0	35.3
Splenic vein	14.50	40.6	5.01	81.0	29.0	35.7
Splenic vein after adrenalin	14.80	46.1	5.43	85.0	27.2	32.1

Spleen weight 240 gm.

Microscopic: Marked pulp congestion; sinuses mostly compressed; quite a few open and empty.

TABLE 4.—CASE 4. ACQUIRED HEMOLYTIC ANEMIA, O. H., ♀, 55

Source of blood	Hgb. in gm. per 100 cc.	Hematocrit %	RBC in mill.per c.mm.	MCV in cu.μ	MCH in mμg.	MCC in %	Fragility H_1	Fragility H_2
Splenic vein	12.8	43.2	4.50	96.0	28.5	29.6	0.52	0.40
Splenic artery	13.0	40.2	4.10	98.1	31.7	32.4	0.50	0.40
Splenic vein after adrenalin	15.0	69.3	7.20	96.3	20.8	21.6	0.54	0.44
Splenic artery after adrenalin	13.8	45.4	4.95	91.7	27.9	30.4	0.52	0.40

Spleen weight 420 gm.

Microscopic: Little or no congestion. Sinuses prominent, containing moderate numbers of erythrocytes, and in many areas large numbers of round cells having the appearance of desquamated sinus endothelial cells. The walls of the sinuses in these areas are denuded. No myeloid metaplasia. Marked hemosiderosis.

TABLE 5.—CASE 5. CIRRHOSIS AND CONGESTIVE SPLENOMEGALY, I. A., ♀, 50.

Source of blood	Hgb. in gm. per 100 cc.	Hematocrit %	RBC in mill.per c.mm.	MCV in cu.μ	MCH in mμg.	MCC in %	Fragility H_1	Fragility H_2
Splenic vein	11.1	33.10	3.61	91.7	30.8	33.5	0.46	0.38
Splenic artery	11.0	33.30	3.60	92.5	30.6	33.1	0.46	0.36
Splenic vein after adrenalin	13.2	59.79	6.10	98.0	21.7	22.1	0.50	0.40
Splenic artery after adrenalin	11.5	38.60	4.00	96.5	28.8	29.8	0.46	0.38

Spleen weight 865 gm.
Microscopic: No evident congestion. Sinuses open and prominent. Diffuse reticular hyperplasia and early fibrosis.

TABLE 6.—CASE 6. CHRONIC MYELOID LEUKEMIA WITH ASSOCIATED MILD HEMOLYTIC ANEMIA, E. V., ♀, 55.

Source of blood	Hgb. in gm. per 100 cc.	Hematocrit %	RBC in mill.per c.mm.	MCV in cu.μ	MCH in mμg.	MCC in %	Fragility H_1	Fragility H_2
Splenic vein	12.2	42.33	4.10	103	29.7	28.8	0.46	0.38
Splenic artery	12.3	42.38	4.18	101	29.4	29.0	0.46	0.36
Splenic vein after adrenalin	14.8	65.32	6.81	96	21.7	22.7	0.48	0.40
Splenic artery after adrenalin	12.5	41.39	4.02	103	31.1	30.2	0.46	0.38

Spleen weight 1390 gm.
Microscopic: Diffuse myeloid metaplasia with numerous megakaryocytes. Considerable pulp congestion. Sinuses compressed.

TABLE 7.—CASE 7. THROMBOCYTOPENIC PURPURA, M. D., ♀, 24.

Source of blood	Hgb. in gm. per 100 cc.	Hematocrit %	RBC in mill.per c.mm.	MCV in cu.μ	MCH in mμg.	MCC in %	Fragility H_1	Fragility H_2
Splenic vein	13.9	43.6	4.20	103.8	33.1	32.1	0.46	0.40
Splenic artery	13.6	37.0	4.06	91.1	31.0	36.6	0.44	0.34
Splenic vein after adrenalin	13.5	43.6	4.45	98.0	30.3	31.1	0.48	0.40
Splenic artery after adrenalin	13.5	41.4	4.10	101.0	33.0	32.6	0.46	0.40

Spleen weight 235 gm.
Microscopic: Normal.

TABLE 8.—CASE 8. THROMBOCYTOPENIC PURPURA, E. R., ♀, 14.

Source of blood	Hgb. in gm. per 100 cc.	Hematocrit %	RBC in mill.per c.mm.	MCV in cu.μ	MCH in mμg.	MCC in %
Splenic vein	12.15	37.0	4.31	85.8	28.2	32.8
Splenic artery	13.15	39.0	4.34	90.0	30.3	33.7
Splenic vein after adrenalin	10.67	38.0	3.84	100.0	27.7	28.0

Spleen weight 152 gm.
Microscopic: Normal.

The data shown in the tables reveal: (1) the marked increase in concentration of red blood cells in the splenic vein blood after injection of adrenalin into the splenic artery in the majority of cases studied; (2) the reduced hemoglobin concentration of the red cells (MCC) under these circumstances. There is little doubt that the

hemoconcentration noted in the splenic vein blood after adrenalin is due to contraction of the spleen and at least partial emptying of the splenic reservoir. The conclusion is inescapable that the necessary preliminary to this phenomenon is a partial separation within the spleen of red cells and plasma, quite in accord with the observations of Knisely[11] and Fåhreus.[9] Whether the circulation is closed[9] or open[15] would appear to be entirely immaterial insofar as a partial separation of red cells and plasma is concerned.

TABLE 9.—CASE 9. CHRONIC NEUTROPENIA WITH SPLENOMEGALY; WISEMAN-DOAN SYNDROME,[17,22] G. M., ♀, 52.

Source of blood	Hgb. in gm. per 100 cc.	Hematocrit %	RBC in mill. per c.mm.	WBC	MCH in mμg.	MCC in %	MCV in cu.μ
Peripheral venous blood 4 hours preoperatively	10.5	34.5	3.75	1,200	28.0	30.40	108.7
Splenic artery	12.0	39.2	3.65	2,600	32.9	30.60	93.1
Splenic vein	12.8	40.0	4.15	2,900	30.8	32.00	103.7
Splenic vein after adrenalin	14.0	43.3	4.83	20,400	29.0	32.15	111.5

Spleen weight 1100 gm.

Microscopic: Touch preparations from the fresh spleen revealed occasional macrophages containing neutrophiles. These were found in larger number in smears of the splenic vein blood, but not in those from the artery. Phagocytosis was not observed in the stained sections of the spleen fixed by injection of Helly's solution. The histologic structure was relatively normal. Moderate congestion of some of the sinuses was observed.

So far as can be determined, the present observations of the marked increase in hematocrit percentage in the splenic vein blood after adrenalin are the first to be recorded for man. Lauda and Haam[13] noted an entirely similar hemoconcentration in the splenic vein blood of dogs after administration of adrenalin. Cruikshank's observations on the cat's spleen have already been referred to.[5] It may be noted further that MacKenzie and his associates[15] have recently described the rapid effect of adrenalin in emptying the pulp of the living cat's spleen of its erythrocytes.

The cause of the above noted reduction in hemoglobin concentration of the red cells cannot be stated with certainty. It is thought probable that an actual loss of hemoglobin from intact red blood cells has occurred during the period of their sequestration in the spleen. The question arose as to whether the reduced hemoglobin concentration of the cells might be only apparent, due perhaps to fragmentation of erythrocytes such as described by Rous and Robertson[19] a number of years ago. Two points argue against this explanation. One is that the presence of fragments was not prominent nor did they appear to have increased after adrenalin as compared with before. In order to account for the marked lowering in hemoglobin concentration, it is believed that fragmentation should really have increased quite obviously. The second point is that the mean corpuscular volume did not vary significantly.

A marked increase might have been expected if fragmentation were important, since under these circumstances the erythrocyte count would be relatively lower than the hematocrit percentage (the fragments would still contribute to the latter, but often, at least, not to the former). An increase in MCV was not observed. Rather than fragmentation, it is thought that the intact or relatively intact erythrocytes suffered an actual loss of hemoglobin. v. Czike[6] was the first to observe that simple sterile incubation of red blood cells *in vitro* resulted in an appreciable degradation of hemoglobin to bile pigment. This observation was confirmed by Barkan[1,2] who has shown that incubation of fresh sterile blood for as little as

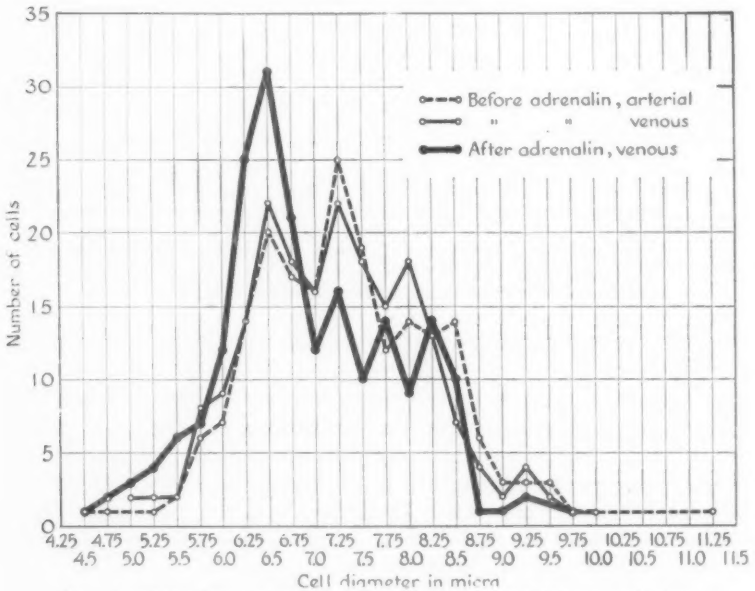

FIG 1.—Price-Jones curves of splenic venous blood before and after adrenalin in Case 3.

6 hours results in significant increases of bilirubin and iron in the supernatant plasma. This phenomenon was correlated by Barkan with the presence of "pseudohemoglobin" and "easily split off" iron in the red blood cells. Barkan's "pseudohemoglobin" and Lemberg's "verdohemoglobin"[14] are probably synonymous, indicating a bile pigment-iron-protein compound intermediary between hemoglobin and bilirubin. In this compound the porphyrin ring of the hemoglobin molecule has opened at the α-methene bridge with the result that a biliverdin-like substance is formed, still in close association with iron and protein. *In vitro*, at least, it has been possible to prepare bilirubin from hemoglobin by this type of transi-

tion.[7,14] To what extent it is important in the *in vivo* formation of bilirubin has not yet been established.

In accordance with previous observations[4] the present study has shown that the erythrocytes in the splenic vein are commonly somewhat more fragile than in the splenic artery, and that this is even more noticeable in the splenic vein blood after adrenalin. The increased spheroidicity correlated with this is typified in the data shown in Figure 1 (Case 3). Whether there is any direct relationship between this characteristic and the reduced hemoglobin concentration of the red blood cells is unknown. That there may be such a relationship is suggested by the fact that the erythrocytes become more spheroidal and less resistant to hypotonic saline on sterile incubation.[3,9]

We have not yet given sufficient attention to the hematocrit percentage and hemoglobin concentration of the red cells in the peripheral blood before and at various intervals after adrenalin. Judging from the present data and from previous observations of hemoglobin and erythrocyte concentration (of the whole blood), it is likely that the reduction in hemoglobin concentration of the red cells as noted in the tables, could often be detected in the peripheral blood. Recently the following data were obtained in a case of aleukemic myelosis with massive splenomegaly:

TABLE 10.—PERIPHERAL BLOOD VALUES IN A CASE OF MYELOSIS BEFORE AND AFTER ADRENALIN

Time	Hgb. in gm. per 100 cc.	RBC in mill. per c. mm.	Hematocrit %	MCV in cu.μ	MCH in mμg.	MCC in %
6-11-42						
Before adrenalin	10.30	3.41	...	...	30.2	
15 min. after adrenalin	10.60	4.13	...	...	25.7	
30 min. after adrenalin	11.20	4.81	...	...	23.3	
1 hour after adrenalin	10.70	4.62	...	...	23.1	
1½ hr. after adrenalin	10.00	3.72	...	...	26.9	
2½ hr. after adrenalin	9.25	3.04	...	...	30.7	
6-17-42						
Before adrenalin	10.15	3.75	33.6	89.8	27.0	30.0
30 min. after adrenalin	11.20	4.65	37.9	81.5	24.1	29.5
1 hour after adrenalin	11.20	4.98	39.1	78.5	22.5	28.6
4½ hr. after adrenalin	10.00	4.18	33.1	79.0	24.0	30.2

In this connection the results of Patek and Daland[18] are of considerable interest. They were unable to establish "significant, sustained changes" of concentration on the basis of hemoglobin, erythrocyte, or hematocrit determinations. It should be noted, however, that they made observations at 5 and 15 minutes after adrenalin and then waited from 45 minutes to 3½ hours, usually 2 to 3 hours, before making additional observations. In our experience the significant increase in hematocrit, hemoglobin, and red blood cells is often not encountered until ½ hour after adrenalin. Little or no change may be observed if the intervals are much

shorter or longer than this, although in some instances the erythrocytosis may be distinct as early as 15 minutes after adrenalin. In Patek and Daland's study of 5 cases of familial hemolytic jaundice, only 1 had anemia, and it is noteworthy that this is the only one in which a significant post-adrenalin erythrocytosis was observed. The findings were as follows in this case:

TABLE 11.—PERIPHERAL BLOOD VALUES IN PATEK AND DALAND'S CASE

Time	Hgb. in gm. per 100 cc.	RBC in mill. per c.mm.	Hematocrit %	MCC in %*
Before adrenalin	7.8	3.10	22.1	35.3
15 min. after adrenalin	10.5	3.88	32.8	32.0
3½ hrs. after adrenalin	7.9	3.00	21.6	36.5

* Calculated by us.

These data, together with the observations in the above case of aleukemic myelosis, suggest that the same red blood cells which enter the circulation at the height of the adrenalin effect, leave it again when the effect has passed. Since there is every reason to think that the spleen is the site of destruction of the more spheroidal erythrocytes, especially in hemolytic jaundice, in which the changes we are discussing are most striking, the likelihood is again supported that there is a direct relationship between increased spheroidocytosis and diminished hemoglobin concentration. Further studies correlating hematocrit percentage, hemoglobin, and red blood cell content and osmotic resistance, before and at suitable intervals after injection of adrenalin, are necessary to determine this point.

It may be noted that no correlation was observed between any particular histologic change in the spleen and the red cell concentration of the splenic vein blood or the hemoglobin concentration of its erythrocytes. In general, the most marked increases in hematocrit percentage and the most outspoken reductions of hemoglobin concentration in the red cells were observed when the spleen was large and congested. In Tables 4 and 6, however, it is seen that there was no evident congestion, yet the hematocrit percentage increased markedly while the hemoglobin concentration of the erythrocytes diminished. It is possible, of course, that splenic contraction might have been sufficient in these instances to expel most of the erythrocytes which had been present before the administration of adrenalin. The partial denudation of the sinus endothelium in many areas of the spleen of Case 4 (Table 4) might be indicative of a recent strong contraction with rapid emptying of the sinuses.

Summary and Conclusions. Studies of the splenic vein blood obtained at the time of splenectomy for various diseases have shown that in many instances a marked increase in erythrocyte concentration occurs after injection of adrenalin into the splenic artery. This increase is associated with a decrease in mean corpuscular hemoglobin concentration, and also with an increase in fragility

and spheroidicity. The exact cause of this decrease in hemoglobin concentration is unknown. It is believed that it may be due to an intracorpuscular degradation of a fraction of the hemoglobin in the intact erythrocytes during the period of their sequestration in the splenic pulp and sinuses, and quite analogous to that observed by Barkan when sterile blood is incubated.

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THE EFFECT OF THE ACCUMULATION OF BLOOD IN THE EXTREMITIES ON THE VENOUS PRESSURE OF NORMAL SUBJECTS.

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Pulmonary edema from cardiac failure develops whenever the right ventricle pumps more blood into the pulmonary vessels than the left ventricle can pump out. Therefore, therapy is largely

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directed towards decreasing the output of the right ventricle. The venous return to the right ventricle may be decreased by quieting the patient with morphine, by phlebotomy and by the application of venous tourniquets to the extremities. The beneficial effect of the accumulation of blood in the extremities by venous tourniquets presumably results from a decreased venous return to the right ventricle as the result of a decrease in venous pressure. Many physicians have believed that in certain patients the accumulation of blood in the extremities by means of tourniquets is as effective as phlebotomy in the treatment of left ventricular failure. The purpose of this study was to determine whether in normal subjects venous accumulation in the extremities produced a significant decrease in venous pressure.

Method. Six normal young males served as subjects. All determinations were made with the subjects in the recumbent position. Twelve centimeter blood pressure cuffs were placed on the upper thighs as close to the trunk as possible. The cloth portion of the cuff was long enough to wrap around the thigh several times. Nineteen-gauge needles were inserted into the external jugular and antecubital veins and the resting venous pressure was recorded by the method of Moritz and Von Tabora[6] using a point 5 cm. beneath the manubrium as the zero point. The needles were kept open by injecting a small quantity of saline at intervals. The blood pressure cuffs on the thighs were then inflated to a pressure of 85 mm. Hg. During this time the venous pressure was recorded every 30 seconds. At the end of 5 minutes the tourniquets were released. Venous pressure readings were recorded until they returned to the resting level.

TABLE 1.—EFFECT OF VENOUS TOURNIQUETS ON THIGHS AT PRESSURE OF 85 MM. HG ON THE VENOUS PRESSURE IN THE EXTERNAL JUGULAR AND ANTECUBITAL VEINS OF NORMAL SUBJECTS.

Subject:	1.		2.		3.		4.		5.	6.
	Venous pressure (mm. of H_2O).									
	Ext. jug.	Ante-cub.	Ext. jug.	Ante-cub.	Ext. jug.	Ante-cub.	Ext. jug.	Ante-cub.	Ext. jug.	Ext. jug.
Resting	100	110	100	135	105	110	105	115	80	110
1 min. after tourniquets	65	85	80	115	90	100	80	100	70	85
2 min. after tourniquets	50	75	60	110	75	100	70	100	45	60
3 min. after tourniquets	45	75	45	110	70	105	70	95	46	40
4 min. after tourniquets	40	70	40	110	65	105	70	95	25	
5 min. after tourniquets	40	70	35	110	65	100	70	100	25	50
½ min. after release	95	110	..	115	100	105	100	115		
1 min. after release	105	120	..	125	105	..	95	110	75	
2 min. after release	100	120	..	130	105	..	95	..	80	110

Results. In 6 normal subjects the average decrease in venous pressure in the external jugular vein produced by the application of venous tourniquets to thighs was 53 mm. of water, the extremes being 65 and 35 mm. of water. The venous pressure fell gradually, reaching a plateau after 2 to 4 minutes. After release of the tourniquets, the venous pressure rose rapidly, reaching the resting level in from 30 to 60 seconds (Table 1).

In 4 subjects the venous pressures in the antecubital and external jugular veins were measured simultaneously. In each instance the pressure in the antecubital vein was higher than that in the external

jugular vein. In these 4 subjects venous tourniquets produced an average fall in venous pressure of only 23 mm. of water in the antecubital vein, while the average decrease in the pressure in the external jugular vein determined at the same time was 50 mm. of water (Table 1).

The application of the venous tourniquets caused little discomfort. There was a slight increase in heart rate during the period of venous accumulation, but the arterial pressure showed little change.

Discussion. The pressure in the external jugular vein was always lower than that in the antecubital vein, and the application of venous tourniquets always produced a greater decrease in venous pressure in the external jugular than in the antecubital vein (Fig. 1). These observations are in accord with those of other investigators who have shown that the antecubital venous pressure does not always vary with the filling pressure of the heart, because the veins of the arm form a collapsible rather than rigid system of tubes.[4,5] It has been demonstrated that no matter how much the intrathoracic pressure is decreased, the venous pressure in the antecubital vein remains positive.[2] The negative intrathoracic pressure collapses the walls of the veins as they enter the thorax and prevents the suction effect of the negative intrathoracic pressure from being transmitted to the blood in the antecubital vein. When the venous pressure is elevated, the column of blood in the antecubital vein becomes continuous with that in the great veins of the thorax. Under these conditions the vein does not collapse in any part of its course, and the pressure in the antecubital vein is the same as that in the right auricle.[1] When the venous pressure is lowered, the vein tends to collapse. It is reopened by the pressure of blood flowing into the antecubital vein from the hand and forearm. Under these conditions, the antecubital venous pressure may not reflect changes in venous pressure in the thorax or auricle. The above-mentioned factors have little influence on the pressure in the external jugular vein, because normally the jugular veins are somewhat distended in the recumbent position. Therefore, on theoretical grounds a decrease in the filling pressure of the right auricle because of a lowering of the venous pressure below the normal level would be expected to produce a greater fall in the pressure in the external jugular vein than in the pressure in the antecubital vein.

Accumulation of blood in the lower extremities by the application of venous tourniquets causes a significant lowering of the venous pressure in normal subjects. The fall in venous pressure is produced primarily by the increase in size of the venous bed in the extremities, although the slight decrease in plasma volume brought about by the high capillary pressure in the extremities may be a minor factor. Ebert and Stead[3] measured the amount of blood present in one upper and two lower extremities before and after venous

congestion. They demonstrated that in the 5 subjects studied, an average of 700 cc. of blood was removed from the head, trunk and arm by placing venous tourniquets on one upper and two lower extremities. This is as much blood as is usually removed during a single venesection.

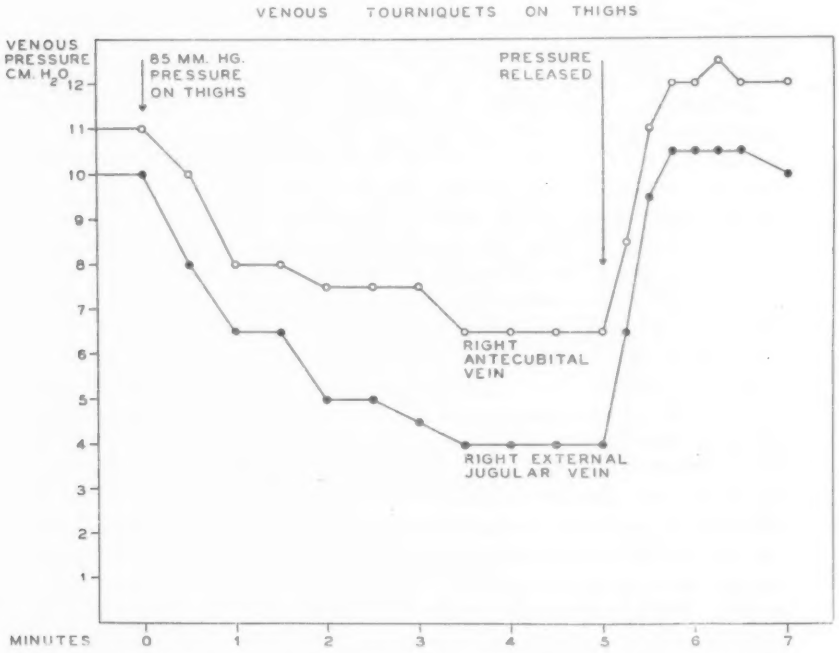

FIG. 1.—The effect of venous tourniquets on the pressure in the antecubital and external jugular veins of a normal subject.

It has been previously pointed out[3] that venous tourniquets are more effective when the systemic venous pressure is normal, when edema of the extremities is absent, and when the patient has been in the recumbent position. If the venous bed in the extremities has already been distended by postural means or by a marked generalized increase in venous pressure, the application of tourniquets will produce little further increase in the size of the venous bed. If the legs are swollen tight with edema, the high tissue pressure will prevent the accumulation of large amounts of blood in the veins. Failure to recognize these limitations in the use of tourniquets accounts for the occasional report that venous tourniquets are ineffective in the treatment of acute left ventricular failure.

Summary. 1. Venous tourniquets at a pressure of 85 mm. Hg were applied to the upper thighs of 6 normal subjects.

2. The application of these tourniquets caused a decrease in

venous pressure in both the external jugular and antecubital veins. The average fall in venous pressure in the external jugular vein was 53 mm. of water. The average fall in venous pressure in the antecubital vein was 23 mm. of water.

3. The decrease in venous pressure from the application of tourniquets to the upper thighs is greater in the external jugular than in the antecubital vein, because the arm veins tend to collapse when the venous pressure is lowered. After the vein walls are in contact, further lowering of the venous pressure proximal to the point of collapse produces no further decrease in venous pressure in the distal portion of the vein.

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PYELOGRAMS IN PATIENTS WITH ESSENTIAL AND MALIGNANT HYPERTENSION

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This study was undertaken in an attempt to answer certain questions in the interpretation of retrograde pyelograms of hypertensive patients who showed no evidence of "surgical" renal disease. These questions were: (1) Is there a pyelogram characteristic of hypertensives? (2) Is the incidence of abnormal urograms in an unselected group of hypertensives greater than in an unselected group of normotensive controls?

A. Characteristics of the Pyelograms of Hypertensives. Voelcker and von Lichtenberg made the first urograms in 1905 but a critical analysis did not appear until 20 years later when Eisendrath and Arens[2,3] called attention to the existence of normal variations. They described three groups of normal pyelograms, *viz.*, ampullary, bifid and pseudospider. The ampullary proved to be the most common group (Fig. 1). When there were two rather distinct divisions of the pelvis from which branched one or more major calyces the pyelogram was classified as bifid (Fig. 5). Those whose calyces

were slender, elongated, and branching were classified as pseudospider (Fig. 4). They found the necks of the major and minor

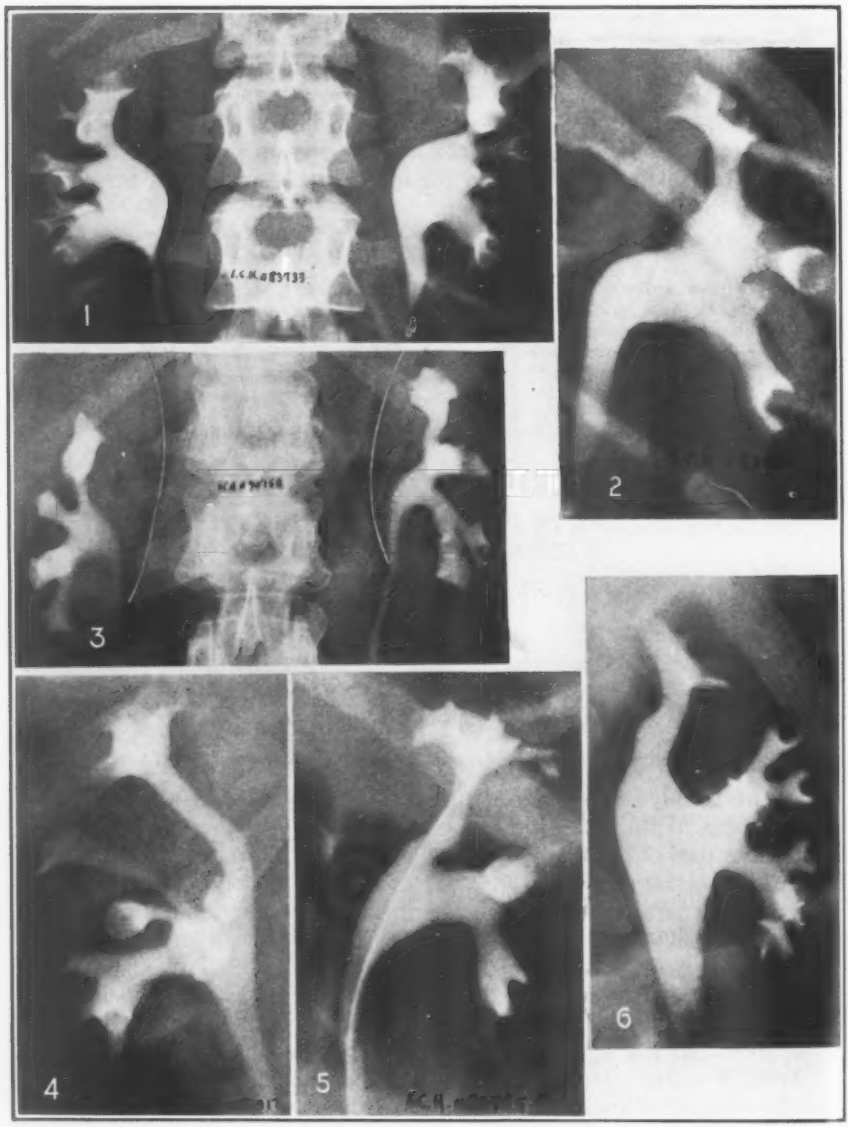

FIG. 1.—Ampullary hilar pelves placed one-half vertebra higher than average.
FIG. 2.—Horizontal, triangular pelvis with right-angled ureteropelvic juncture.
FIG. 3.—Bilateral intrarenal pelves placed one-half vertebra higher than average.
FIG. 4.—Pseudospider type pelvis showing long slender calyces.
FIG. 5.—Bifid type pelvis.
FIG. 6.—Extrarenal pelvis.

calyces were usually quite narrow but with much variation. The calyces could be so large that the pelvis proper was only visible as a small portion of the pyelogram, and conversely the pelvis often predominated over the calyces. Changes in shape of the ureter, pelvis and calyces due to peristalsis were emphasized.

In the same year Goldstein and Carson[5] showed that normal ureters have diameters of 2 to 5 mm., and the normal pelvis measures 2 x 2 cm., with an average capacity of 8 ml. varying from 3 to 13 ml.

Moody and Van Nuys[10] examined 450 healthy university students with antero-posterior roentgenograms of the abdomen and reported the most common position of the kidney to be opposite the first 4 lumbar vertebræ when erect. When supine, the cephalic pole lay opposite the 12th thoracic and the caudal pole opposite the 3d lumbar vertebræ.

In 1933 Rose, Hamm, Moore and Wilson,[18] from a critical analysis of 385 pyelograms defined a normal renal pelvis as one symmetrically placed in the kidney, with free flow of urine through its parts.

The so-called "intrarenal" pelvis may be defined as one in which the renal tissue wholly surrounds it and the ureteropelvic juncture is seen in the Roentgen photograph as part of the medial border of the shadow of the kidney (Fig. 3). By contrast, the ureteropelvic juncture in a kidney with a "hilar" pelvis is separated from the medial border with the pelvis partly within it. Occasionally the pelvis appears to be outside the kidney, making the intrarenal portion seem to consist entirely of calyx ("extrarenal" pelvis) (Fig. 6).

Method. In an attempt to answer the first question we have limited our study to patients with *normal* retrograde pyelograms as judged by the criteria suggested by the authors cited above, and by Wesson and Ruggles.[25] The borderline between normal and pathologic, in brief, depends upon a separation of all pyelograms exhibiting signs of stasis, infection, displacement, lithiasis, filling defect, or congenital anomaly. These criteria will be discussed more fully in the section on results. In order to facilitate analysis, each pyelogram was inspected for certain characteristics:

1. Location of renal pelvis as to whether it was intrarenal, extrarenal, or hilar.
2. Level of renal pelvis in relation to vertebral landmarks.
3. Renal torsion; complete or incomplete rotation.
4. Presence or absence of a right-angled ureteropelvic juncture.
5. Capacity of the pelvis as judged from the comparative size of the shadow.*
6. Size of calyces in relation to pelvic size.
7. Number of minor calyces.
8. Configuration of calyces and infundibuli.
9. General shape of pelvis; triangular, square or rounded.
10. Axis of renal pelvis; normal oblique, horizontal or vertical.
11. Tendency toward intrarenal duplication of pelvis (bifid pelvis).

* Retrograde pyelograms were made by the gravity method.

The retrograde pyelograms of 100 hypertensive patients were compared with the pyelograms of 100 normotensive individuals. Most of these were made by one of us (J. M. Y.) and were considered to be within normal limits by the roentgenologist, the urologist and the authors of this paper.

We arbitrarily selected 149 mm. systolic and 89 mm. Hg diastolic as the upper limits of normal arterial pressure.

Results. The results are summarized in Table 1.

1. The renal pelvis of adults is usually hilar and in this, hypertensive subjects do not differ from normotensives. Further, the difference in the incidence of bilateral intrarenal pelves is only 4%. When those with unilateral intrarenal pelves are included, the difference is 3%.

2. The ureteropelvic juncture usually is at the level of the 2d lumbar transverse process with the right pelvis placed 2 or 3 cm. below the left. The limits of normal motility were set at one vertebra above and below this point. Very few pyelograms were seen where the juncture was higher than the 1st lumbar transverse process when supine. Those in which the juncture fell below a line through the 3d transverse processes when supine or erect were classified as abnormal. Occasionally, even though the kidney did not descend this low when erect, angulation of the ureter indicated an abnormal degree of ptosis.

The series is too small for statistical analysis but it is noteworthy that kidneys placed lower than average occurred twice as frequently in hypertensives and higher than average on one or both sides in 42% of normotensives, as compared to 30% in the hypertensives.

3. Renal torsion apparently is the result of incomplete rotation of the kidney. It was present in 11% of hypertensives and 8% of normotensives. We believe that partial rotation is a normal variation if unassociated with signs of stasis or infection. Dilatation of the calyces (calyectasis), dilatation of the pelvis (pyelectasis), or blunting of the calyces were regarded as signs of stasis, and shagginess or blurring of the calyceal outline as signs of infection.

4. When the axis of the pelvis meets the ureter at approximately a 90 degree angle it is designated a right-angled ureteropelvic juncture (Fig. 2). Such pelves usually have a horizontal axis and are roughly rectangular in shape. If, with this finding stasis was suggested by high insertion of the ureter, aberrant renal blood-vessel, calyectasis, ptosis, ureteropelvic stricture or an angle of less than 90%, the pyelogram was considered abnormal. The incidence of right-angled ureteropelvic junctures was the same in each class of patients.

5. The average capacity of the renal pelvis is generally believed to be 6 to 9 ml. Otherwise normal pelves may hold as much as 20 ml. In reading pyelograms it is customary for urologists and roentgenologists to make a notation if the pelvis appears small or

large. Wesson and Ruggles[25] advise against interpreting the outline of a pelvis as abnormal unless the evidence of pyelectasis is beyond question. We distinguish early hydronephrosis from a pelvis which is merely large by the presence of blunting of the calyces and/or bulging as indicated by convex superior and inferior borders. Such pyelograms were considered abnormal. Normal pyelograms were grouped according to the relative size of their pelves.

Non-hydronephrotic pelves larger than average were found almost twice as frequently in hypertensives.

6. We noted the size of the pelvis in relation to the size of the calyces because it has been suggested,[18,25] that a pelvis small in proportion to the calyces tends to cause back pressure. Pyelograms which showed large branching major calyces with comparatively small pelvic reservoirs were classed as smaller than average. Those films that showed short, stubby minor calyces with indefinite major calyces, so that the pyelogram seemed to be almost all pelvis were recorded as larger than average. A pelvis of average size in relation to the size of the calyces occurred with equal frequency in hypertensives and normotensives.

7. The minor calyces may vary in number from 6 to 15.[7] In a retrograde pyelogram it is difficult to count them all as a few may be obscured. We arbitrarily considered those showing between 8 and 13 minor calyces per kidney as exhibiting an average number. There was no significant relationship between the number of minor calyces and the existence of hypertension.

8. The superior calyx is usually long and thin while the inferior calyx is often short and stumpy.[25] The position of the pelvis within the kidney affects the length of the major and minor calyces. There are definite changes in the size and contour of the calyces, due to their peristaltic activity—short and broad calyces becoming long and narrow. Therefore, variations in the configuration of the calyces may not be regarded as permanent. A narrow, elongated infundibulum may merely be a transient peristaltic wave and not an impediment to drainage. Irrespective of these difficulties in interpretation we thought it interesting to record the character of the calyces. There was no relationship between the pelvic configuration and hypertension.

9. As seen in Figure 1 the renal pelvis has a triangular outline. The base of the triangle parallels the long axis of the kidney. In certain pyelograms the pelvis assumes a rectangular appearance while more rarely the outline is rounded and roughly spherical. In both hypertensives and normotensives the general shape of the pelvis was triangular in 9 out of 10 pyelograms.

10. The axis of the pelvis corresponds to the height of the pelvic triangle. This usually meets the axis of the ureter at an angle of 130 to 150 degrees. If the angle is more acute than this we have classed it as a horizontal pelvis. If the angle approaches 180 de-

grees, the pelvis is classed as vertical. The pelvic axis of hypertensives does not differ from normotensives.

11. A bifid pelvis is one showing a tendency to intrarenal duplication in that there are two divisions of the pelvis from each of which may branch 1 to 3 major calyces. There is no significant difference in the incidence of bifid pelves in the two classes of patients.

TABLE 1.—SUMMARY OF ANALYSIS OF NORMAL PYELOGRAMS OF 100 HYPERTENSIVES AND 100 NORMOTENSIVES

Pyelographic characteristics	Classification of normal variations	Number	
		Hypertensives	Normotensives
1. Location of renal pelvis	Hilar pelves bilaterally	59	62
	Intrarenal pelves bilaterally	20	16
	One hilar, the other intrarenal	16	17
	Extrarenal	3	4
	Uncertain	2	1
2. Level of renal pelvis	Average level	53	48
	Higher than average: Unilat.	10	14
	Higher than average: Bilat.	20	28
	Lower than average: Unilat.	10	3
	Lower than average: Bilat.	5	4
	One pelvis high, other low	2	3
3. Renal torsion (kidney rotation)	Complete rotation	89	92
	Incomplete rotation: Unilat.	11	8
	Incomplete rotation: Bilat.	0	0
4. Presence of right-angled ureteropelvic junct.	Normal ureteropelvic juncture bilaterally	76	78
	Right-angled ureteropel. junct. bilaterally	7	3
	Unilat. rt.-angled ureteropel. junct.: R	15	18
	Unilat. rt.-angled ureteropel. junct.: L	2	1
5. Capacity of renal pelvis	Average	61	66
	Smaller than average	21	24
	Larger than average	18	10
6. Size of pelvis in relation to size of calyces	Average	64	65
	Smaller than average	22	19
	Larger than average	14	16
7. Number of minor calyces	Average	92	89
	More than average	3	6
	Fewer than average	5	5
8. Character of calyces	Not unusual	63	63
	Predominance of long, narrow infundibuli	22	24
	Predominance of short, stubby calyces	15	13
9. General shape of renal pelvis	Triangular pelves bilaterally	90	92
	Rectangular pelves: Unilat.	8	2
	Rectangular pelves: Bilat.	0	2
	Rounded pelves: Unilat.	1	4
	Rounded pelves: Bilat.	1	0
10. Axis of renal pelvis	Normal axis bilaterally	67	69
	Horizontal: Unilat.	13	15
	Horizontal: Bilat.	10	10
	Vertical: Unilat.	7	5
	Vertical: Bilat.	2	0
	One horizontal, other vertical	1	1
11. Type of renal pelvis	Neither pelvis bifid	72	67
	Bifid pelvis: Unilat.	11	12
	Bifid pelvis: Bilat.	17	21

B. Incidence of Renal Abnormalities in Essential and Malignant Hypertension. In order to determine whether abnormalities of the urogram are more common in hypertensive than in normotensive patients, we considered the following data:

1. The incidence of hypertension in patients who exhibited easily recognizable renal abnormalities as judged by retrograde pyelograms.

2. The incidence of the same degree of renal abnormalities in an unselected group of hypertensive patients.

3. The average mean arterial pressure of patients with abnormal pyelograms as compared with the average mean pressure of those with normal pyelograms.

To determine the correlation between abnormal pyelograms and associated elevated arterial pressure, we reviewed 218 consecutive retrograde pyelograms made at the Indianapolis City Hospital during the past year. Each pyelogram was classified as normal or abnormal and the blood pressure of the patient noted. Retrograde urography is performed routinely on all hypertensive patients studied at the Lilly Clinic. This group was considered separately from the above.

Results. One hundred pyelograms exhibiting obvious abnormalities such as hydronephrosis, ptosis, filling defects, polycystic disease, ureteropelvic constriction, calculus or congenital anomalies were studied. Of this group, 78 were normotensive and 22 were hypertensive. Criteria for the occurrence of hypertension in the general population seldom are the same, thus making it difficult or impossible to compare one investigation with another. Our problem was to determine the incidence of hypertension in the population of a general hospital. Whether this differs from that in the supposedly healthy civilian population we do not know. Braasch, Walters and Hammer[1] found that 19.4% of 869 admissions to the Mayo Clinic (ages 20 to 70) had systolic pressures of 145 mm. of mercury or above. Oppenheimer, Klemperer and Moschkowitz[11] selected every 15th patient in a series of 5000 who came to autopsy and observed high blood pressure in 24%. In general, a blood pressure of 155/95 mm. Hg or more was considered the criterion of hypertension. Shure[23] selected at random 947 of 11,898 autopsy reports and found 34.9% had a persistent arterial pressure of 150/95 or above.

Recognizing that there is no general agreement as to the incidence of hypertension we believe that an incidence of 22% in our 100 patients with abnormal urograms (age group 20 to 60) is not significantly greater than that in the general hospital population.

The average arterial pressure of 122 patients with gross renal abnormalities as judged by retrograde urography was compared with the average arterial pressure of 96 persons with normal pyelograms. The results were summarized in Table 2.

The urograms of 114 unselected patients who came to the Lilly Clinic complaining of hypertension were reviewed and classified. The results are summarized in Table 3. The borderline cases were those with questionable blunting of the calyces, or questionable dilation of the pelvis and calyces.

Unfortunately it is practically impossible to find a comparable control series because the number of normotensives showing significant renal abnormalities is high in those who must be cystoscoped.

Comment. A normal pyelogram does not conclusively rule out the presence of renal disease, but when abnormal it usually indicates a moderately extensive lesion. The interpretation of pyelograms is often uncertain due to lack of generally accepted limits of normalcy. This paucity of normal criteria is partly due to limitations of description. The aphorism, "One picture bespeaks a thousand words," is nowhere more apt.

TABLE 2.—COMPARISON OF AVERAGE ARTERIAL PRESSURES OF PATIENTS WITH ABNORMAL AND WITH NORMAL PYELOGRAMS

	Average systolic arterial pressure, mm. Hg	Average diastolic arterial pressure, mm. Hg	Average mean arterial pressure, mm. Hg
122 patients with grossly abnormal pyelograms	129	81	105
96 patients with normal pyelograms	131	81	106

TABLE 3.—PYELOGRAMS OF 114 HYPERTENSIVE PATIENTS

	No.	%
Normal	84	73 68
Borderline	8	7 03
Abnormal	22	19 29
Total	114	100 00

Retrograde urography has certain well-known advantages over the excretory method. Minor degrees of deformities are delineated more clearly. According to Wesson and Ruggles,[25] "One who depends upon intravenous pyelograms alone and does not check the diagnosis by a complete kidney investigation is going to make costly blunders."

Ravich[15] using this method concluded that hypertension is almost invariably associated with kidneys having an intrarenal pelvis. In our series 61% of hypertensives failed to show an intrarenal pelvis. Sarnoff[24] reported an incidence of 40% intrarenal pelves in 50 hypertensives. Hyman and Schlossman[6] found no higher incidence among hypertensive than normotensive patients.

Riskind and Greene[16] recently reported a case of hypertension associated with postural unilateral renal torsion. We have found 4 normotensives who exhibited unilateral failure of rotation plus signs of stasis of a degree to be considered abnormal. Our series suggests that incomplete rotation occurs with equal frequency in normotensives.

Attempts have been made to classify all cases of essential hypertension according to the predominant associated syndrome. Williams and Harrison[26] and Schroeder and Steele[20] distinguish five groups: (1) renal; (2) nervous; (3) vascular; (4) endocrine; and (5) unclassified. This follows the classification of Page[12] except for the fifth group which is limited to essential and malignant hypertension. McCann[9] goes so far as to hypothesize that in 80% to 85% essential hypertension depends on atheromatous narrowing of the

larger renal arteries and in the remainder the trouble is due to unsuspected disorders of the kidneys or urinary passages.

Schroeder and Steele[21] found excretory urographic abnormalities in 50 of 71 essential hypertensives. In another series of 178 cases[22] which includes these 71 patients, 71 (45%) showed abnormal excretory urograms. Schroeder[19] considered as abnormal 37 intravenous urograms of 50 patients exhibiting slight elevation of blood pressure. Slight hydronephrosis was the most frequent lesion noted. Our results differ from theirs in two regards: (1) the incidence of hypertension in a hospital population is believed by us to be greater than suggested by them, and (2) our results were obtained by comparing a normal with a hypertensive group of patients.

Braasch, Walters and Hammer[1] found the incidence of hypertension among 1684 patients with surgical condition of the kidney to be no higher than in a similar group of people taken at random. Friedman, Moschkowitz and Marrus[4] showed that the mean blood pressure and incidence of hypertension was no greater in a group of 193 patients nephrectomized for unilateral renal disease than in a comparable control series.

Maher and Wosika[8] found only 17% of 600 patients with hypertension to have abnormalities of the urinary tract and kidneys of sufficient degree to remove them from the category of essential hypertension. The specific lesions included prostatic hypertrophy as the most frequent, pyelonephritis, urolithiases and combinations of obstruction and infection. It is noteworthy that such conditions usually are expressed by urographic anomalies especially if they have progressed to such a degree as to contribute to, or cause, hypertension. Therefore, the urogram should be a fairly reliable method for detecting such cases.

Pearman, Thompson and Allen[14] present evidence indicating an incidence of renal lesions of 3.2% in 12,000 instances of hypertension.

Palmer, Chute, Crone and Castleman[13] reported significant urographic abnormalities in 22% of 212 hypertensives.

Ritter[17] observed hypertension in 14.2% of 28 patients with urinary developmental anomalies. He reviewed the histories of 24 patients suffering from hydronephrosis or renal anomalies with or without stone or secondary infection and found none to be hypertensive after an interval of 5 to 10 years.

It is our impression that the range of normal variation in urograms is wider than usually recognized. Questionable pyelographic variations in normotensives are often disregarded while the same variations in hypertensives are emphasized—the patient then becoming a "renal" hypertensive.

Summary and Conclusions. The retrograde pyelograms of 100 hypertensives and 100 normotensives were studied to ascertain whether hypertension was associated with any constant pyelographic variation. Those which seemed more common in hypertensives

were: (1) renal pelves which were larger than average, and (2) pelves whose position was lower than average. Intrarenal pelvis, incomplete rotation (renal torsion), right-angled ureteropelvic juncture, and bifid pelvis were no more common than in normotensive patients. Hypertension was not associated with any significant variation in the size of the pelvis to the size of the calyces, the general configuration of the pelvis, the pelvic axis, nor the number or morphology of minor calcyes.

The incidence of hypertension in patients who exhibited easily recognizable renal abnormalities as demonstrated by retrograde pyelograms was 22%. The average mean arterial pressure of patients with abnormal pyelograms was the same as the average mean pressure of those with normal pyelograms. The incidence of significant renal abnormalities in an unselected group of hypertensives was 19%.

The retrograde pyelograms of patients with essential hypertension do not differ significantly from those of normotensives. The incidence of urographic abnormalities in an unselected group of hypertensives appears to be no greater than in normotensives.

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CARDIAC CIRRHOSIS

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Cardiac cirrhosis usually is defined as hepatic fibrosis due to congestive heart failure.[1,2] In order to preclude the possibility that borderline cases might be included, this study of cardiac cirrhosis was limited to instances of hepatic fibrosis of such a degree as to cause actual architectural distortion of the liver. All cases of Laennec's cirrhosis and fibrosis due to infection were excluded. Only patients who died of congestive heart failure were studied, in order that there could be no question of the likelihood that significant passive hyperemia of the liver had been present.

The material for the study consisted of the clinical and pathologic observations on 790 consecutive, adult, autopsied patients in whom heart disease was the chief cause of death. These cases occurred in 6548 consecutive postmortem examinations done at the Cleveland City Hospital in the decade from January 1930 to December 1939 inclusive. Thirty-five instances of cardiac cirrhosis were encountered.

The Incidence of Cardiac Cirrhosis in Various Types of Heart Disease. The incidence of cardiac cirrhosis varied with the type of heart disease (Table 1). It is evident that cardiac cirrhosis occurred most often in rheumatic heart disease and hypertensive heart disease. Thus 119 patients who died primarily of rheumatic heart disease included 14 (11.8%) with cardiac cirrhosis. Of 264 patients who died primarily of hypertensive heart disease, 14 (5.3%) had cardiac cirrhosis. The remaining 407 patients (who died of a variety of other types of heart disease) included 7 instances of cardiac cirrhosis (1.7%).

Clinical Features. *Number of Episodes of Heart Failure, Splenomegaly, Ascites, Valvular Lesions and Jaundice.* The number of cases is not large enough to permit statistical analysis, but certain tendencies are demonstrable.

There was a tendency for cardiac cirrhosis to occur in patients who had had more than one episode of heart failure. The 14 patients with cardiac cirrhosis who died of rheumatic heart disease included 9 (64%) who had had more than one episode of heart failure. The remaining 105 patients who died of rheumatic heart disease but who did not have cardiac cirrhosis, included 38 (36%) who had had multiple failures. Of the 14 patients dying of hypertensive heart disease and showing cardiac cirrhosis, 6 (43%) had had more than one episode of heart failure. Of the 250 patients who died of

hypertensive heart disease and who did not have cardiac cirrhosis, 69 (28%) had more than one episode of heart failure.

There likewise was a tendency for splenomegaly to be associated with the cases of cardiac cirrhosis. This was best shown in the group of patients dying of rheumatic heart disease. Of the 14 patients with cardiac cirrhosis, 11 (79%) had a spleen weighing over 200 gm. whereas of the 105 patients without cardiac cirrhosis 26 (25%) had a spleen weighing over 200 gm.

In regard to ascites, in the rheumatic heart group, of the 14 patients with cardiac cirrhosis, 11 (79%) had ascites either clinically or at autopsy. Of the 105 patients without cardiac cirrhosis, 45 (43%) had ascites either clinically or at autopsy. In the case of the patients dying of hypertensive heart disease, of the 14 suffering from cardiac cirrhosis, 9 (64%) had ascites; of the 250 who did not have cardiac cirrhosis, 100 (40%) had ascites.

Study of the nature of the valvular lesions in the 119 patients who died of rheumatic heart disease showed that of the 14 who had cardiac cirrhosis, 4 (29%) also showed tricuspid stenosis. Of the 105 patients without cardiac cirrhosis, only 9 (9%) had tricuspid stenosis. Stated differently, of the 13 patients who had tricuspid stenosis, 4 (31%) had cardiac cirrhosis.

Jaundice did not occur frequently enough to permit study.

Diagnosis. It is difficult to diagnose cardiac cirrhosis clinically. The material at hand seems to indicate that the condition occurs more often in patients with heart disease of some standing. It occurs especially in patients with rheumatic heart disease or hypertensive heart disease, and relatively often in individuals with tricuspid stenosis.

The presence of a liver smaller than one would expect in the face of congestive failure, the existence of ascites and splenomegaly not attributable to other causes are suggestive evidence. However, in the clinical appraisal of a given case, this evidence could be misleading since all of these signs can occur in a patient without cardiac cirrhosis.

In the 35 cases studied, the diagnosis was made in only 5 cases. The report of the case in which the clinical diagnosis seemed most justified is as follows:

Case Study. J. G., a colored man aged 42, entered Cleveland City Hospital January 5, 1934. He had had shortness of breath on exertion and occasional swelling of the ankles for 8 months.

Examination showed a well-developed, well-nourished negro. He was short of breath. The cervical veins were distended. There were râles at the bases. The heart was enlarged in all directions and showed a systolic murmur at the apex. The cardiac mechanism was normal. The blood pressure was 220 systolic and 140 diastolic. The liver was tender and the edge was 6 cm. below the costal margin. There was no ascites. The extremities, scrotum, sacral and lower abdominal regions showed pitting edema. The retinal arteries were thin and tortuous, and venous nicking was present.

The patient received digitalis and diuretics, and improved. He was discharged February 10, 1934. The diagnosis was hypertensive heart disease and myocardial insufficiency.

He was again admitted to the hospital July 17, 1934, because of marked myocardial insufficiency. The findings were as before except that ascites was present. He improved and was discharged November 22, 1934.

The patient was admitted to the hospital the third time April 23, 1935. There was evidence of marked myocardial insufficiency. Abdominal paracentesis was done on 2 occasions. The edge of the liver was 5 cm. below the costal margin. He was discharged May 27, 1935.

He was admitted to the hospital a fourth time July 30, 1935. Shortness of breath and anasarca had returned. During this admission, because of ascites which recurred despite the frequent use of mercurial diuretics, abdominal paracentesis was done 9 times. The patient finally became free of edema, and was discharged February 22, 1936. The diagnosis of cardiac cirrhosis was made on this admission.

The patient was admitted to the hospital the fifth time April 17, 1936. He was moribund and died in 12 hours.

In a period of about 28 months, the patient had spent 407 days in the hospital. He had suffered varying degrees of myocardial insufficiency for over 3 years. The clinical diagnosis was hypertensive heart disease, myocardial insufficiency and cardiac cirrhosis.

Autopsy. Autopsy was performed by Dr. Gallavan 83 hours after death. The body was normally developed and showed marked anasarca.

The abdominal cavity contained 6300 cc. of serous fluid, the right pleural space 125 cc., the left pleural space 130 cc., the pericardial sac 300 cc.

The heart weighed 850 gm. and was dilated. The coronary arteries showed rather marked arteriosclerosis.

The liver was of normal shape and weighed 1875 gm. The edges were moderately rounded. The capsule was opaque and thickened. The organ cut with increased resistance. The surface was a mottled brownish-red color. It was difficult to distinguish hepatic lobules.

The other viscera showed chronic passive hyperemia. There was generalized arteriosclerosis.

TABLE 1.—THE FREQUENCY DISTRIBUTION OF CARDIAC CIRRHOSIS IN THE VARIOUS TYPES OF HEART DISEASE

Type of heart disease	No. of cases	No. with cardiac cirrhosis	%
Hypertensive heart disease	264	14	5 3
Coronary heart disease	177	3	1 7
Rheumatic heart disease	119	14	11 8
Syphilitic heart disease	67	1	1 5
Cor pulmonale	54	1	1 9
Subacute bacterial endocarditis	31	0	0 0
Acute bacterial endocarditis	13	0	0 0
Thyroid heart disease	9	0	0 0
Calcific aortic stenosis	9	0	0 0
Obliterative pericarditis	7	1	14 3
Tuberculous pericarditis	7	0	0 0
Pericardial adhesions	5	1	20 0
Miscellaneous	9	0	0 0
Undiagnosed	19	0	0 0
	790	35	4 4

Microscopically, the architecture of the individual lobules of the liver could be made out but there was considerable distortion due to extensive fibrosis. This fibrous tissue was in most situations quite young as it stained poorly with Van Gieson's stain but vividly with Heidenhain's stain. The

fibrosis was most marked in the subcapsular areas where it was diffuse. Otherwise there was no constant distribution. There was considerable chronic passive hyperemia and the central veins were markedly distended.

The diagnosis was generalized arteriosclerosis, cardiac hypertrophy and dilatation, cardiac cirrhosis* and chronic passive hyperemia of the viscera.

Summary. Of 790 consecutive, adult, autopsied patients who died of heart disease, 35 (4.4%) had cardiac cirrhosis. Only those cases were included in which there was actual architectural distortion of the liver.

Cardiac cirrhosis occurred essentially in two types of heart disease, *viz.*, rheumatic heart disease (14 of 119 cases) and hypertensive heart disease (14 of 264 cases).

From a clinical standpoint there was a tendency for the cases of cardiac cirrhosis to be associated with multiple episodes of failure, ascites, splenomegaly and in the rheumatic group with tricuspid stenosis. In 5 of the 35 cases studied, the diagnosis was suspected clinically. It appears that there are no definite criteria, however, which permit the consistent clinical diagnosis of cardiac cirrhosis.

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STUDIES ON THE PENETRATION OF SULFONAMIDES INTO THE SKIN

I. Penetration of Sulfonamides from Various Ointment Bases into the Intact Skin of Guinea Pigs; and a New Method of Analysis of Tissue Sulfonamides†

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In a previous paper,[2] we presented the first analytical data, to our knowledge, on rates of penetration of sulfonamides into the intact skin from various vehicles. These data were derived from

* Diagnosis of Dr. H. T. Karsner, Chief of the Department of Pathology of Cleveland City Hospital.

† Supported by grants from the General Research Fund of the University of Minnesota; and from the Abbott Laboratories, North Chicago, Ill. Assistance was furnished by the personnel of Work Projects Administration, O. P. 165–1–71–124, Subproject 383. We wish to express our gratitude for the extensive assistance of our wives, Gertrud and Lois.

direct tissue analyses of the skin of rabbits, rats and humans, after various periods of applications of sulfonamides in wet packs, ointments, and by iontophoresis.

One of us[4] had previously attempted to determine the degree of liberation of the incorporated sulfonamide from various ointment and jelly bases into agar plates streaked with staphylococci, as judged by measured clear areas free of bacterial growth. It is now realized that this approach cannot be justifiably extended to clinical practice, since it shows only the partition coefficient between the vehicle and the agar. Although it does give some information regarding the degree of liberation of the incorporated sulfonamide, this information does not necessarily apply to the skin. Since it is of practical importance to have a better comparison of what can be obtained regarding the tissue concentration of sulfonamides diffusing from various vehicles, it was decided to examine the tissue concentrations produced by various ointment bases containing different concentrations of sulfonamides.

From the previous report[2] it was indicated that in regard to penetration of sulfonamides, rat skin was more similar to human skin than the more delicate rabbit skin. As it was impossible for the purposes of this study to use human subjects, because of the large number of cases needed, and the multiple biopsies required for each subject, we selected guinea pigs rather than the rat, as it was impossible to keep dressings or bandages on rats. Several experiments with rats immobilized in confining cages showed skin penetration rates of sulfanilamide quite comparable with those of guinea pigs and humans.

Methods. The experimental animals were guinea pigs ranging in body weight from 400 to 600 gm. The hair along the back and sides was clipped with a fine electric hair clipper, taking care not to injure the skin. The ointments were applied to the skin and held in place with gauze bandages and adhesive tape. The animals were placed in narrow confining cages which made it impossible for them to disturb the bandages, yet permitted them to take food (cabbage) placed before them. In order to study the effect of time and concentration on penetration, ointment was applied to two areas, separated by the vertebral column. These areas extended along the sides of the animal, precautions being taken to prevent the ointments applied to each area, from intermixing. The ointments were reapplied once daily.

Biopsies were performed after 1, 2 and 3 days, to obtain the time effect. When concentration effects were being studied, ointments of two different concentrations of sulfanilamide (SNA)* were applied to the same animal, one on the left area, and the other on the right.

Prior to performing biopsies, the animals were thoroughly washed with soap and warm running water, after which the areas to be biopsied were shaved and rinsed. A piece of skin approximately 4 to 8 sq. cm. was removed with scissors under light ether anesthesia, cutting down to the panniculus carnosus muscle layer. The excised skin pieces were washed

* Supplied through the courtesy of Dr. D. F. Robertson, of Merck & Co., Inc., Rahway, N. J.

with soap and running warm water, blotted, and pinned to sheet cork. Uniform skin aliquots weighing approximately 60 to 100 mg. were punched out by means of a sharp blow delivered to a cylindrical brass punch, approximately 1 cm. in diameter. They were weighed immediately on a torsion balance and analyzed for total sulfanilamide.

Method of Chemical Analysis of Tissue Sulfanilamide. Tissue SNA was first determined by a method previously described,[2] in which free SNA was analyzed in tissue filtrates from ground tissue, by the method of Bratton *et al.*,[1] using a photoelectric colorimeter.

The photoelectric colorimeter was designed and built after the Evelyn type instrument.[3] It contained a Mazda flashlight bulb and metal reflector as the light source, controlled in intensity by a vernier rheostat combination; a General Electric barrier type photoelectric cell,* linear within 1% up to 50 microamperes (the maximum photoelectric current generated was less than 3 microamperes); and a Leeds-Northrup galvanometer (type KS5410), with a period of 3 seconds or less, a resistance of ca. 1000 ohms, a critical damping resistance of 5000 to 10,000 ohms, and giving a full-scale deflection at 2.5 microamperes. The entire instrument, including the galvanometer and lamp and scale, is housed in a small box, 9 x 7 x 13 inches, and cost approximately $100 to construct. The aluminum house holding the light source, filter holders, absorption cuvette, and photoelectric cell, is similar to that described by Evelyn[3] except that the filter holder was adapted to hold the less expensive Standard Corning and Wratten 2 inch filters, and the cuvette holder contained a microadaptation for smaller test tube cuvettes, of dimensions 11 mm. inside diameter, 1 mm. wall thickness, 10 cm. long, and optically selected. Readings could be made with 3 cc. volumes.

Bratton *et al.*[1] describe the absorption maximum of SNA solutions after color development by their method, which is essentially the method we used, as 5450 Å units, whereas we found it to be 5421 Å, as determined both in a special Zeiss single monochromator photoelectric spectrophotometer, and in the Coleman single monochromator spectrophotometer. The curve was quite broad, however, varying not more than 2% transmission from the maximum when extended 50 Å units in either direction from the maximum. When we chose a Corning filter combination which gave a maximum transmission close to the absorption maximum of the SNA solution, namely 5425, difficulty was had because the filter absorbed too much light, and a good curve could not be obtained. Finally a filter combination of Corning filters No. 3486, 5120, and 4303, was selected, which followed Beer's law with standard SNA solutions, up to 0.3 mg. % concentration. This filter combination gave a maximum transmission at 5521 Å units, varying only about 2%

* General Electric Catalogue No. 4120833-9-1.

transmission when shifted 50 Å units in either direction from the maximum.*

In determining large numbers of tissue SNA concentrations, it was found time-consuming and cumbersome to grind the tissues, especially skin, in a mortar with sand, prior to filtration and analysis, as described previously.[2] Hence another method of analysis was developed, which permitted large numbers of determinations to be made each day. Tissue aliquots are macerated and taken into solution by HCl hydrolysis in a hot water bath, cooled, precipitated with trichloracetic acid, filtered, and the filtrate analyzed for SNA.

Procedure. The weighed biopsy was placed into a 10 cc. volumetric flask, 3.5 cc. 0.6 N HCl were added from a burette, and the flask partially immersed in a boiling water bath, by means of a wire basket holder, for 30 minutes, after which the tissue was completely macerated and taken into solution upon vigorous (!) shaking. Longer boiling tends to produce discoloration, and subsequent errors. Two cc. 15% trichloracetic acid was added, making the solution 3% in trichloracetic acid, and the flask filled to volume with distilled water. After thoroughly shaking, the solution was filtered through a fine grained analytical filter paper (7 cm. No. 589 ashless Schleicher and Schüll) in a 1.5 inch short-stemmed funnel. Five cc. of the clear filtrate was analyzed for SNA by the method of Bratton *et al.*,[1] modified to meet the conditions of our experiments. To 5 cc. of the filtrate were added: (1) 0.5 cc. freshly prepared 0.1% $NaNO_2$ (Merck, AR). Shake and leave 3 minutes. (2) 0.5 cc. 0.5% ammonium sulfamate (La Motte, pure cryst.). Shake and leave 2 minutes. (3) 0.5 cc. 0.1% n(1-naphthyl)-ethylene diamine dihydrochloride (Eastman No. 4835). Shake and leave at least 5 minutes. Keep in the dark until readings are made. It fades somewhat after an hour. The percentage transmission was then determined in the photoelectric colorimeter, and converted to mg. per 100 cc. from standard calibration charts. Recoveries of known added amounts of SNA to tissue aliquots were determined to ascertain the experimental treatments necessarily followed to yield accurate results, varying the boiling time, acid concentration, size of tissue aliquots, and concentration of SNA.

Table 1 illustrates typical results of recoveries of known added amounts of SNA to 80 to 100 mg. rat skin aliquots, using the methods prescribed above.

Many different techniques of washing off excess ointments prior to performing biopsies were tried before it was found best to use soap and warm water, followed by shaving. At least 100 animals were used, and several hundred skin analyses performed, before we

* We wish to acknowledge the assistance of Mr. I. Rusoff, of the Department of Physiological Chemistry, University of Minnesota; and Mr. D. Clausen, of International Milling Company, Minneapolis; who made the determinations on several sulfonamide solutions.

were able to apply an SNA ointment, wash it off immediately and find no skin SNA on analysis of biopsies. The technique described under "Methods" consistently proved satisfactory.

TABLE 1.—RECOVERY OF KNOWN ADDED SULFANILAMIDE FROM RAT ALIQUOTS (80-100 MG. WET WEIGHT)

Mg. Sulfanilamide

Added	Recovered
0.00	0.00
0.01	0.00995
0.01	0.01
0.02	0.0195
0.02	0.0196
0.03	0.03
0.03	0.0299

Ointment Bases. Seven different ointment bases were arbitrarily selected on the basis of their previous usage. Three were of the oil-in-water emulsion (O/W) type, and 4 of the water-in-oil emulsion type (W/O). The following ointment bases were used:

O/W	A.	Sodium lauryl sulfate	1.0
		Stearyl alcohol	10.0
		Cetyl alcohol	3.0
		Spermaceti	10.0
		Glycerol	10.0
		Water	60.0
	B.	Liquid petrolatum	57.0
		Peanut oil	3.0
		Triethanolamine	2.0
		Stearic acid	4.0
		Cetyl alcohol	2.8
		Water	71.2
	C.	Stearyl alcohol	20.0
		Mineral oil	20.0
		Petrolatum	60.0
		Water	20.0
W/O	1.	"Hydrosorb"* (Abbott). A base consisting of oleic acid, white petrolatum, oleic acid ester and amide of diethanolamine.	
	2.	Equal parts of white petrolatum and lanolin.	
	3.	"Aquaphor"† (Duke). A base consisting of esters of cholesterol mixed with petrolatum.	
	4.	Cod-liver oil	20.0
		Lanolin	20.0
		Petrolatum	60.0

* Furnished to us for experimental use by Abbott Laboratories, North Chicago, Ill.
† Furnished to us for experimental use by the Duke Laboratories, Inc., Stamford, Conn.

Sulfanilamide powder was incorporated in 1%, 5% and 10% concentration in each ointment.

Results. The results are summarized in Table 2. Each figure represents averages of at least triplicate determinations (3 skin aliquots) from one piece of skin from each animal for each concentration of SNA, and for each time. The numbers of animals used for each ointment are indicated in the table. A total of 54 animals

were used, representing at least 600 separate analyses. In many cases more than 3 aliquots were taken from each skin biopsy.

TABLE 2.—PENETRATION OF SULFANILAMIDE (SNA) INTO INTACT SKIN OF GUINEA PIGS FROM VARIOUS OINTMENTS

	Type of emulsion						
	Oil-in-water			Water-in-oil			
Ointment base	A	B	C	1	2	3	4
Number of animals	4	6	4	27	5	4	4
1% SNA ointment —av. mg. per 100 cc. SNA in skin, after:							
1 day	3.3	4.7	1.8	3.7±1.1	2.3	1.4	1.3
2 days	..	..	..	8.0±0.8			
3 days	5.3	5.5	3.5	7.8±2.3	3.3	2.3	2.9
5% SNA ointment —av. mg. per 100 cc. SNA in skin, after:							
1 day	4.7	4.3	3.3	5.2	2.5	2.0	2.4
3 days	5.9	5.3	4.5	10.4	5.2	3.0	4.3
10% SNA ointment —av. mg. per 100 cc. SNA in skin, after:							
1 day	..	..	..	4.3±1.5			
2 days	..	..	..	10.3±1.9			
3 days	..	..	..	11.5±2.3			

Scrutiny of Table 2 reveals that SNA penetrates the intact skin more from Base 1 ("Hydrosorb") than from the other bases. Since this base permitted the best penetration of SNA, we chose it for a more exhaustive examination of the effect of time and concentration, as indicated by the number of animals used.[7] To demonstrate even more strikingly a possible concentration effect, 10% SNA was compared in this base, with 1% for 1, 2 and 3 days.

It is seen that although there is a tendency for increasing concentration of SNA to cause greater skin concentrations, this effect is much less marked and less consistent than the effect of time.

The second conclusion to be drawn from the results is that there is no correlation between the penetration of SNA and the type of ointment base used, at least with respect to whether the emulsion type was oil-in-water or water-in-oil.

There are individual animal differences, and it was for this reason that the large number of animals was used in the case of Base 1, to justify the use of averages. These individual differences are best seen by the probable errors expressed for the results for Base 1, in Table 2.

Discussion. During recent times, many reports have been made of the use of topically applied sulfonamides in the treatment of pyogenic skin infections, infected burns, and so forth. Variable results have been obtained, which have been discussed elsewhere.[5,6,7] To our knowledge, the present paper presents the first objective study of penetration of a sulfonamide from ointments into skin or tissue. Heretofore workers in this field have selected ointment bases and the concentration of the incorporated sulfonamide purely by personal preference. Our results show clearly that this type of selection is without meaning, at least with respect to SNA and our

special experimental conditions. It would be futile to investigate all the numerous ointment bases which have been recommended and discussed in the medical literature, by the method herein described, since we believe we have shown that there is no logical choice to be made on the basis of present knowledge.

Only a given quantity of SNA is taken up by the skin from the bases within a given time period, and this amount cannot be increased by increasing the concentration in the ointment.

Some preliminary experiments have been performed on intact human skin, using techniques identical to the animal work described above. The results have shown that skin concentrations obtained with corresponding concentrations of SNA in the same bases used are essentially of the same order, justifying in our opinion the extension of the results obtained from animal work to the human.

It is conceivable that an effect of concentration of SNA in an ointment could increase the skin penetration, by more frequent applications. In our work, only one daily application was made.

The human experiments are being extended, and will be reported at a later date, along with the results obtained with other sulfonamides.

Summary. 1. The rate of penetration of sulfanilamide into the intact skin of guinea pigs from 4 typical water-in-oil and 3 oil-in-water emulsion ointment bases has been determined by direct chemical analyses of skin biopsies, with respect to time and concentration of sulfanilamide.

2. A new method of tissue sulfanilamide analysis has been described, which permits large numbers of analyses of total sulfanilamide to be determined in a relatively short time.

3. There is no correlation between the penetration of sulfanilamide and the type of ointment base, at least in regard to whether the base is of the water-in-oil or the oil-in-water emulsion type.

4. Increasing the concentration of sulfanilamide in ointment bases above 1% has little effect on tissue levels of SNA reached.

5. Increasing the time of application of sulfanilamide consistently increased the tissue levels reached.

6. Preliminary human experiments indicate that the results of the animal experiments may be justifiably extended to the human.

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CHOLESTEROL IN THE LUNG AND SERUM OF NORMAL PNEUMONIC RATS

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It is well known that in certain infections the concentration of cholesterol in the serum undergoes characteristic changes. This has been borne out by the work of Denis[3] and Kipp[5] among the early workers and subsequently by Shope,[11] Marino,[7] McQuarrie and Stoesser,[8,13] Stoesser,[14] and Steiner and Turner[12] and others. The latter authors generally found that the change in total serum cholesterol concentration is due to variations in the ester fractions, the free fraction remaining fairly constant. Some of the writers and notably Kipp have speculated that the change reflects a mobilization of cholesterol from the blood stream to the site of infection. As the only direct evidence supporting this thought we have the report of Kubota[6] who states, in a very brief résumé of his work, that in the pneumonic tissue of the rabbit the total cholesterol concentration was "remarkably increased." Suggestive evidence is seen in the work of Christian[2] who found two distinct types of fat in pneumonic exudations. Indirect evidence suggesting a mobilization of cholesterol in infection appears in the work of Boyd[1] who found an increase of free cholesterol in the leukocytes of the circulating blood during infections, and in the report of Frola[4] who noted a general diminution in the ester cholesterol of the viscera during the course of experimental peritonitis.

It was the purpose of this experiment to study simultaneously the changing status of free and ester cholesterol in the serum and diseased tissue of rats in which experimental pneumococcus lobar pneumonia has been induced as an anatomically localized, readily accessible infection.

Materials and Method. The experiment was performed upon adult male albino rats supplied from a well-inbred colony and ranging in weight from 180 to 270 gm. The animals were fed the regular stock diet used in this laboratory and received water *ad libitum*.

A Type III pneumococcus culture was supplied by Dr. Francis Gunn, in whose laboratory this strain has served for years in the production of satisfactory rat pneumonias.

Pneumonia was induced in the animals by the technic of Nungester and Jourdonais.[9]

Serum cholesterol determinations were done by the method of Schoenheimer and Sperry.[10] The modification of Sturges and Knudson[15] was employed for the estimation of tissue cholesterol.

Procedure. The rats were inoculated in three groups. At intervals spaced to follow the known course of the disease, groups of animals were

killed. Just prior to killing, several cc. of blood was withdrawn from each by cardiac puncture to supply material for serum cholesterol determination. The entire lobe in which the consolidation appeared was removed for analysis.

Results. *A. Normal Controls.* Serum cholesterol fractions in 26 normal animals are shown in Table 1. The mean value for free cholesterol is seen to be 13.3 mg. per 100 cc., with a standard deviation of ±2.131 mg. per 100 cc. The mean value for total cholesterol is 49.7 mg. per 100 cc., with a standard deviation of ±7.36 mg. per 100 cc. The mean free in total ratio is 26.7% with a standard deviation of ±2.61%.

TABLE 1.—NORMAL CONCENTRATION OF CHOLESTEROL IN THE SERUM

Rat No.	Free (mg. per 100 cc.)	Total (mg. per 100 cc.)	Free in total %
1	10.6	42.2	25.1
2	14.3	52.2	27.3
3	14.8	57.7	25.7
4	15.5	54.8	28.2
5	15.1	54.9	27.5
6	14.7	58.2	25.3
7	11.0	41.5	26.5
8	10.6	36.6	29.8
9	14.0	49.0	28.6
10	11.0	34.4	32.0
11	13.5	54.0	25.0
12	11.5	49.0	23.5
13	14.1	55.4	25.5
14	14.0	52.0	26.9
15	13.0	46.8	27.8
16	16.4	53.6	30.3
17	12.7	47.3	26.9
18	12.4	49.0	25.3
19	16.0	58.0	27.6
20	19.3	60.4	31.9
21	13.2	57.4	23.0
22	14.1	62.9	22.3
23	11.2	53.3	21.0
24	10.7	43.0	25.0
25	13.6	50.8	26.8
26	10.5	38.6	27.2
Mean	13.3	49.7	26.7
Standard dev.	±2.131	±7.36	±2.61

Tissue cholesterol fractions in 13 normal left lobes are shown in Table 2. Because of the difference in size of the animals the values have not been treated statistically but it is clear that in the range of sizes employed in this experiment the total amount of cholesterol in the left lobe is well in excess of 1 mg. and less than 2 mg. However, the per cent of ester in total cholesterol is independent of the quantity of tissue analyzed and so has been treated statistically. The mean ester/total ratio for 13 left lobes and three groups of right-sided lobes is 5.69%, with a standard deviation of ±1.84%.

Tissue cholesterol data are reported as absolute amounts rather than mg. per unit dry weight owing to the fact that technical diffi-

culties in drying the consolidated lobes made the latter figures unreliable.

TABLE 2.—NORMAL CONCENTRATION OF CHOLESTEROL IN THE LEFT LOBE

Rat No.	Free (mg.)	Total (mg.)	Ester in total %
1	1.47	1.59	7.5
2	1.59	1.67	4.8
3	1.72	1.86	7.5
4	1.67	1.81	7.5
5	1.60	1.69	5.7
6	1.83	1.90	4.2
7	1.56	1.62	3.7
8	1.56	1.68	6.8
9	1.69	1.80	5.9
10	1.60	1.78	9.8
11	1.51	1.59	5.4
12	1.83	1.97	6.8
13	1.76	1.86	5.7
Mean	1.64	1.74	
	RIGHT LOBES		
A	3.00	3.14	4.6
B	2.94	3.05	3.8
C	3.41	3.60	5.5
Mean			5.69
Standard deviation			±1.84

(Rat A above was a normal animal. Rats B and C had extensive left lobar consolidations and apparently normal right-sided lobes.)

B. Pneumonic Animals. In about half the animals the inoculating catheter slipped into the lobe situated behind the heart rather than the left lobe. This made a considerable difference in the quantity of tissue being analyzed in each case, the former being a much smaller lobe. For this reason the tissue results are reported separately. However, for the general purposes of this experiment it made little difference where the consolidation was located. The sites and estimated extents of the pneumonias which served as material for this report are given in Table 3.

TABLE 3.—SITES AND EXTENTS OF THE CONSOLIDATIONS

Involvement, %	Left lobe	Post-cardiac lobe
100 to 75	4	10
75 to 50	4	4
50 to 25	7	5
Less than 25	2	1

The behavior of the serum cholesterol fractions is shown in Figures 1, 2 and 3. The data are superimposed on the previously established normal means and bands describing ±3 standard deviations from those means. It is seen that there are no statistically significant changes in either of the fractions despite a clearly expressed tendency toward diminution of the ester fraction (rising free in total ratios) early in the course of the disease, best shown in Figure 3.

The behavior of the tissue cholesterol fractions is shown in Figures 4, 5 and 6. A progressive accumulation of cholesterol is noted from the time of inoculation, with maximum concentrations between the 6th and 9th days. By the 14th day, at which time only a slight discoloration over the area usually occupied by the consolidation remained as evidence of past pneumonia, a return to

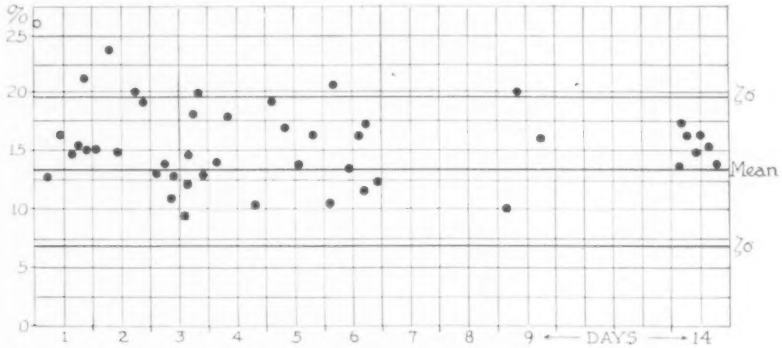

FIG. 1.—Serum-free cholesterol during pneumonia in rats. Mean of 26 normals $\pm 3\sigma$.

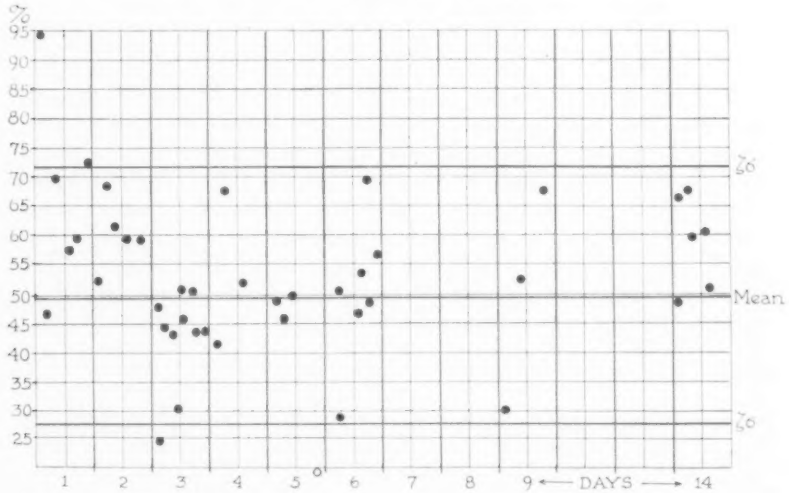

FIG. 2.—Serum total cholesterol in rats during pneumonia. Mean of 26 normals $\pm 3\sigma$.

normal values is seen. The increasing relative length of the ester portion of the lines is noteworthy. This disproportionate increase of esters in the face of rising values for free cholesterol is best shown in Figure 6. Here again the data for ester in total ratios are superimposed upon the normal mean for 13 animals, with ± 3 standard deviations from that mean.

Discussion. In each group of animals some degree of consolidation existed in all subjects and on any given day the age of the lesions was constant, but in no 2 animals was the extent of the consolidation identical. Since the entire lobe was analyzed in each case, it follows that within certain limits the tissue ester in total ratio was affected by "dilution" with variable amounts of normal lung tissue. Such tissue has been shown in Table 2 to contain about 95% cholesterol and 5% esters. While this variation is noteworthy, the total amounts of cholesterol recovered from the pneumonic lungs when compared with the total amounts recovered from the normal lungs make it relatively of less importance.

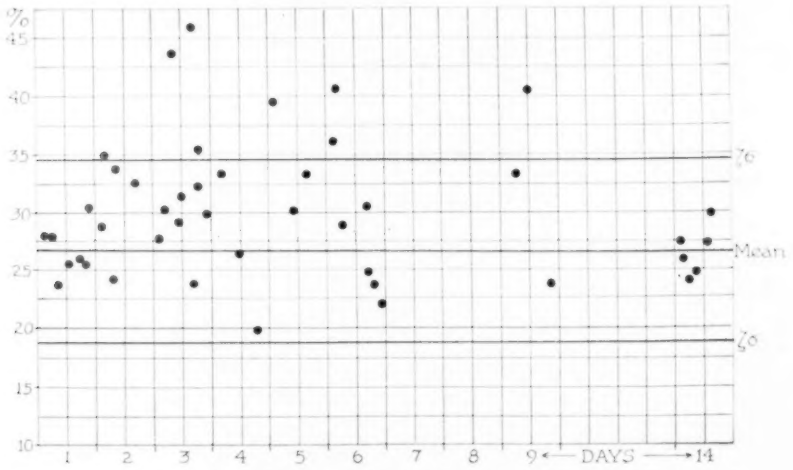

FIG. 3.—Serum-free/total cholesterol ratios during rat pneumonias. Mean of 26 normals $\pm 3\sigma$.

The fact that the serum cholesterol was frequently normal despite extensive accumulations of cholesterol in the lung suggests that the serum is not the ultimate source of the sterol. If involved at all it probably operates as an agent in the transport from tissue depots, and, in certain subjects, maintains a normal serum-free/ester equilibrium in doing so. It is noted that only the lung was analyzed in this study.

As to the origin of the cholesterol that accumulates in the diseased tissues it is probable that multiple sources are involved. The red blood cells, the leukocytes and the serum that find their way into the exudate all are known to contain generous quantities of cholesterol, chiefly in the free state.

There is no present explanation for the daily increase in the ester fraction of the tissue cholesterol. Unless one is to postulate a selective retention of esters from the blood circulating through the con-

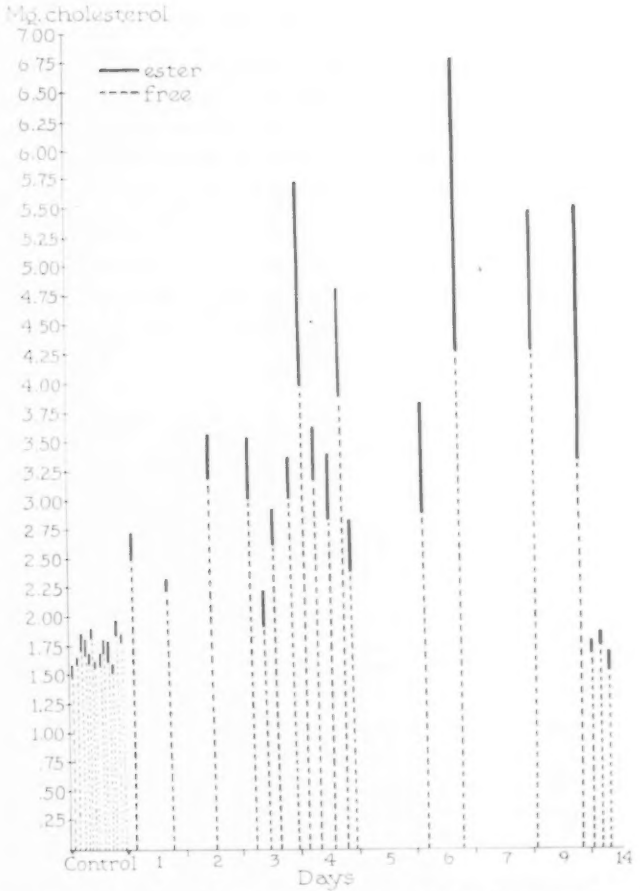

FIG. 4.—Absolute amounts of cholesterol present by days in the pneumonic left lobes of rats.

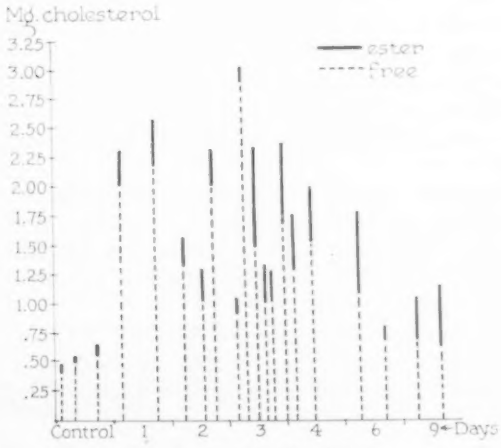

FIG. 5.—Post-cardiac lobes.

solidated area, one must consider the possibility of enzymatic action to explain the progressive apparent esterification. This possibility is the subject of further work currently being done in this laboratory.

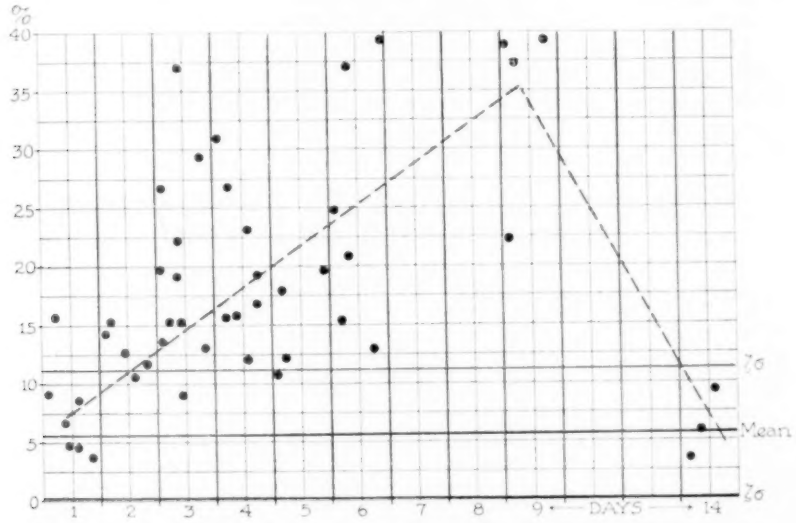

FIG. 6.—Ester/total ratio of cholesterol in pneumonic lobes arranged by days after inoculation (rats).

Summary and Conclusions. Pneumococcus lobar pneumonia was induced in healthy adult albino rats. On specified days after inoculation, groups of the animals were bled from the heart and killed. The sera and diseased lobes were analyzed at once for the cholesterol fractions.

Except for occasional instances early in the course of the disease both free and total cholesterol in the serum remained unchanged.

There was a tendency for the proportion of ester to free cholesterol in the serum to fall. This is expressed as a trend toward increasing free in total ratios early in the course of the disease.

There was a striking absolute increase in the total cholesterol present in the diseased lobe during the course of the pneumonia. This increase involved both free and ester fractions but not in equal or constant degrees.

There was a progressive increase in the proportion of ester cholesterol in the diseased lung during the course of the disease.

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THE EFFECT OF ADRENALINE AND SYMPATHOMIMETIC AMINES UPON TOTAL BODY WATER

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THERE are few drugs which have been studied more extensively in the pharmacologic laboratory than has adrenaline and yet many phases of its therapeutic action are incompletely understood. One of these is its relief of symptoms in several types of allergic reactions. In recent years, a number of papers have been published in which it has been shown that variations in water metabolism may affect the development of allergic reactions.[9,12,14,16,17] The suggestion in these and related reports is that changes in water balance do not *cause* allergic reactions but may affect the *susceptibility* of the body to allergens. The hypothesis is succinctly stated by Kern[12] as, "Water and salt retention will favor the development of allergic reactions." While not all agree with Kern's generalization, yet there seemed to be sufficient evidence to warrant a study of the effect of adrenaline and related sympathomimetic amines upon water metabolism.

The most commonly known effect of adrenaline upon body water is its diuretic-antidiuretic reaction originally described by Bardier and Fraenkel in 1899. This reaction has been demonstrated in most vertebrates except the aglomerular fishes[18] and is composed of two reactions, an initial renal vascular reaction of brief duration and secondly a more prolonged effect upon body water-salt metabolism. The initial antidiuretic-diuretic renal vascular reaction is well known and is related to the marked sensitivity of the renal blood-vessels to adrenaline. The second reaction extends over a period of 1 or 2 hours or more, and during it there is a redistribution of

water and salt in the body. The exact changes vary with species of animal, dosage of adrenaline, the state of water balance and other factors. In essence, however, there occurs a loss of water and certain salts from blood and tissues due to an increased output in urine and possibly other channels of excretion.[2,4,6,8,10,11,13,19,20]

In previous reports, the effect of adrenaline upon water metabolism has been described in terms of its effect upon the rate of urine formation. Changes in total body water do not necessarily parallel changes in the rate of urine formation, and the object of the present investigation was to measure the effect of adrenaline upon total body water. If allergic attacks are associated with retention in tissues of body water, as suggested by Kern[12] and others, then adrenaline might conceivably improve the symptoms if it were to have a dehydrating effect. This latter was found to occur.

The animal selected for this study was the frog because it has a very labile water metabolism. In most higher vertebrates, water conservation is so well developed that it is difficult to demonstrate small effects upon total body water. In the frog, the exchange of body water may be as great as 5% of its body weight per hour.[5] Several authors have previously reported that adrenaline has no effect upon the total body water of frogs[1,3,7] but their studies were limited to few animals and a narrow range of doses. As the studies herein reported progressed, it became obvious that a wide range of doses of adrenaline would have to be studied and that large numbers of animals would be needed to bring out the relatively minor and variable dehydrating effect of small doses of the drug.

Leopard frogs, *Rana pipiens*, were used. The animals were acclimatized to room temperature in water overnight, then taken out of water, the urine expressed, the skin carefully dried and body weight determined to the nearest 0.1 gm. on a trip scale balance. Adrenaline hydrochloride in various doses, dispensed in its pharmacopeial (B.P.) vehicle, was injected into the dorsal lymph sac. Control animals received the same volume of the vehicle without the adrenaline hydrochloride. The frogs were then placed in 400 ml. beakers covered with weighted glass shields and body weight determined again at hourly intervals. From 25 to 75 frogs were used to find the effect of each dose of adrenaline hydrochloride. The doses studied were from 10^{-25} to 100 mg. per kilo body weight at geometric increments of 10.

Doses of adrenaline hydrochloride less than 10^{-12} mg. per kilo body weight had no effect upon body water. Doses of adrenaline hydrochloride from 10^{-12} to 10^{-5} mg. per kilo had no consistent effect upon body water for 1 hour, but in the second hour they consistently increased the loss of body water by from 20% to 40%. These results are shown in Figure 1, in which the mean difference in the loss of body water in frogs given adrenaline hydrochloride over that in the controls has been expressed as a percentage of the

loss of water in the controls. After the second hour, there again was no consistent effect of adrenaline upon body water.

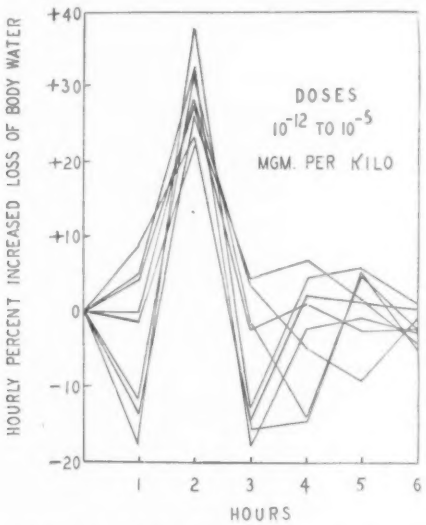

FIG. 1.—The effect of small doses of adrenaline hydrochloride upon the rate of loss of total body water in frogs.

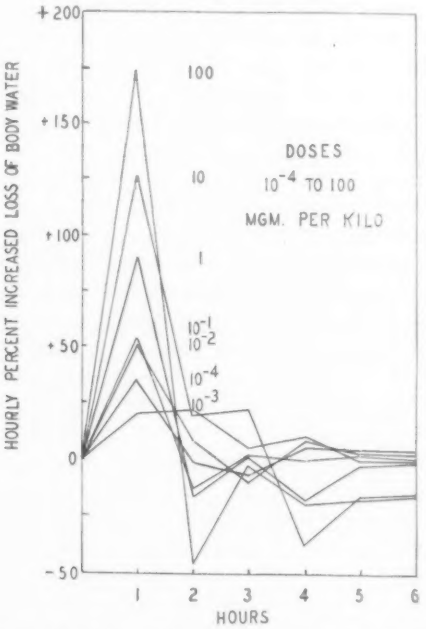

FIG. 2.—The effect of pharmacopeial and larger doses of adrenaline hydrochloride upon the rate of loss of total body water in frogs.

In the larger doses, adrenaline produced an immediate increase in the loss of body water during the first hour after administration as seen in Figure 2. The increase varied from 25% greater than the control value in frogs receiving 10^{-4} and 10^{-3} mg. per kilo body weight of adrenaline hydrochloride, to as much as 175% greater than the control loss of body water in frogs receiving 100 mg. of the drug per kilo. After the first hour, adrenaline had less consistent effects, tending in most groups to have a slight hydrating effect. The recommended pharmacopeial dose of adrenaline hydrochloride corresponds in man to about 10^{-2} or 10^{-3} mg. per kilo subcutaneously, doses which in frogs caused a definite increase in the loss of body water.

These results indicate that adrenaline causes in the frog a stimulation of the loss of body water which may extend over from 1 to 2 hours. The beneficial effect of adrenaline in allergic disorders may perhaps be explained as, in part at least, a stimulation of water loss. The failure of adrenaline therapeutically in certain allergic reactions or allergic-like reactions such as salicylism may be due to such reactions being not necessarily associated with water retention because, of course, water retention is not the only factor concerned in allergic reactions.

Seasonal Variations. Reactions involving shifts in body water often vary with the seasonal shifts in body water. Thus, for example, the Brunn reaction in frogs, which consists of an uptake of body water by frogs kept in water when injected with posterior pituitary extract, disappears almost entirely in the cold winter months in this locality. With this seasonal variation in mind, adrenaline hydrochloride was given at approximately monthly intervals to groups of 30 frogs at varying doses over a period of 1 year. The dehydrating action of adrenaline could be demonstrated and to the same degree with corresponding doses at all seasons of the year.

Ergotoxine Ethanesulphonate. Experiments were next designed to find if ergotoxine ethanesulphonate would inhibit or reverse the dehydrating effect of adrenaline in frogs and the mean results have been charted in Figure 3. Ergotoxine ethanesulphonate alone was injected subcutaneously into a total of 312 frogs in doses of from 10^{-5} to 100 mg. per kilo body weight with the result that there was a consistent retention of body water over a period of 2 hours with all doses, an effect the opposite to that of adrenaline. In a second series of frogs, the animals were given injections of similar doses of ergotoxine ethanesulphonate and then an injection of adrenaline hydrochloride of 1 mg. per kilo body weight. In these latter experiments, the ergotoxine reduced to some extent the dehydrating effect of adrenaline but did not completely inhibit it nor reverse it.

Ergotamine Tartrate. In contrast to the hydrating effect of ergotoxine, ergotamine had no consistent effect upon frog body water in

subcutaneous doses of from 10^{-3} to 10 mg. per kilo body weight. In experiments upon some 300 frogs, there were no significant changes in body water with these doses of ergotamine tartrate which was used in the form of Gynergen, N.N.R. Nor did ergotamine have any effect upon the dehydrating action of adrenaline in experiments arranged as described for ergotoxine.

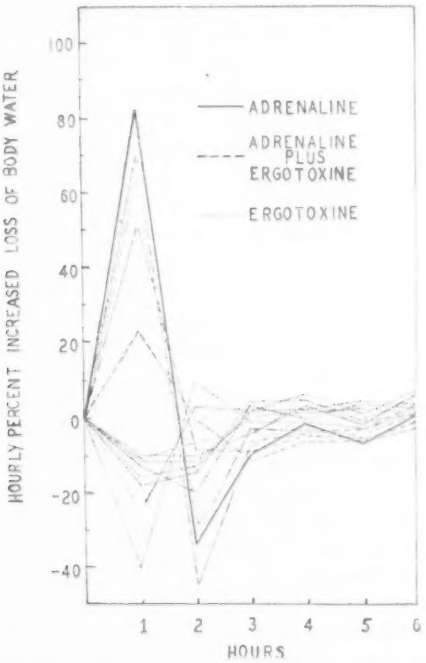

FIG. 3.—The effect of ergotoxine upon the rate of loss of total body water in frogs and upon the dehydrating action of adrenaline hydrochloride.

The difference in the response of frog body water to ergotoxine on the one hand and to ergotamine on the other is of considerable interest pharmacologically because these two alkaloids are almost identical in a qualitative, pharmacologic sense and differ only in a few reactions quantitatively.[15] Clinically, the two drugs are used for almost identical purposes, except in the therapy of migraine where ergotamine is the drug of choice. Migraine is classified by many as an allergic disease and, if Kern's hypothesis is correct, the above findings may indicate at least one reason why ergotamine is used apparently in preference to ergotoxine clinically in migraine. That is, while ergotamine does not dehydrate like adrenaline, it does not hydrate like ergotoxine, which latter would presumably be an advantage in migraine.

Ephedrine Hydrochloride. Ephedrine hydrochloride was given hypodermically to 330 frogs in the same manner as adrenaline hydrochloride and inidoses of from 10^{-2} to 100 mg. per kilo body weight. It had no sgnificant effect upon the rate of loss of body water.

Betaphenyl-n-propylamine Hydrochloride. Ephedrine is a derivative of betaphenyl-isopropylamine and adrenaline of betaphenyl-ethylamine. The corresponding n-propylamines have not been studied to the same extent. One of these latter, betaphenyl-n-propylamine hydrochloride was placed at our disposal by Dr. E. Gifford Upjohn of the Upjohn Company with data suggesting that it might be useful in the therapy of bronchial asthma. It was injected into frogs in doses of from 10^{-2} to 100 mg. per kilo body weight in a manner similar to that with adrenaline hydrochloride. In the larger doses of 10 and 100 mg. per kilo, it produced an increased loss of body water which averaged 30% greater than the loss of body water in the controls during the first hour after injection. This effect corresponded to that of adrenaline hydrochloride in doses of about 10^{-3} or 10^{-4} mg. per kilo body weight. In doses of 1 mg. per kilo and less, this n-propylamine had no consistent effect upon body water. The drug was thus similar qualitatively but not quantitatively to adrenaline in its effect upon body water.

Summary. Adrenaline hydrochloride was found to have a dehydrating effect in the frog. Doses of from 10^{-12} to 10^{-5} mg. per kilo body weight speeded up by from 20% to 40% the loss of body water during the second hour after subcutaneous injection. Larger doses up to 100 mg. per kilo body weight increased the loss of body water during the first hour after injection by amounts up to nearly 200% of the water loss of controls.

Ergotoxine ethanesulphonate had the opposite effect, causing a retention of body water for a corresponding period and when given with adrenaline hydrochloride, it decreased to some extent, but did not eliminate or reverse the dehydrating action of adrenaline.

Ergotamine tartrate and ephedrine hydrochloride in corresponding doses had no effect upon frog body water.

Betaphenyl-n-propylamine hydrochloride had a dehydrating effect similar to that of adrenaline hydrochloride but requiring relatively much larger doses to yield a corresponding effect.

The possible relation of these findings to the use of adrenaline in allergic states is discussed.

The authors wish to acknowledge with thanks the coöperation, financial and otherwise, of Mr. C. H. Wilkins of the British Drug Houses (Canada) Limited, of Dr. E. G. Upjohn of the Upjohn Company and of the Wingate Chemical Company of Montreal.

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THE THROMBIC ACTIVITY OF A GLOBULIN FRACTION OF THE PLASMA PROTEINS OF BEEF, SWINE AND HUMAN BLOOD

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Parfentjev[3] recently published an observation that by a salting-out procedure there could be obtained from rabbit plasma a pseudoglobulin fraction having marked coagulation activity on normal human oxalated blood. We have investigated this pseudoglobulin fraction and have shown that it is thrombic in nature,[6] can be used as an excellent hemostatic in small wounds[2] and is effective in decreasing the coagulation time of the circulating blood when administered by mouth in relatively large doses.[5] The present communication presents evidence that the same material can be obtained from the plasma of human, steer and swine blood.*

Methods. Blood was obtained directly from the jugular veins of steers and collected in an equal volume of 2.5% sodium citrate in 0.9% sodium chloride. The blood was centrifugalized, and the supernatant plasma drawn off. In most instances, a mixture containing equal parts of ether and phenol was added as a preservative, 10 ml. of this preservative being added for each liter of plasma. Human plasma likewise contained this preservative.

* In a letter dated December 29, 1941, Dr. A. G. Hogan of the University of Missouri reported to us that he had obtained, using our methods, an active thrombin preparation having 20 Smith units per mg. of nitrogen from oxalated swine blood.

Two samples of swine plasma were obtained through the courtesy of the Lederle Laboratories. One of these plasmas was prepared by mixing 30% potassium oxalate with blood in the proportion of 1 to 100. The other sample of plasma contained 6% of a 46% solution of sodium citrate as an anticoagulant. No preservative was present in either preparation of swine plasma.

The procedure used was that of Parfentjev[3] as standardized in this laboratory[6] for the preparation of rabbit thrombin. Except where variations were made for reasons discussed below, the beef, human and swine plasmas were precipitated 3 times with 20% ammonium sulphate; the combined filtrates precipitated twice with 30% ammonium sulphate; and the final precipitate dissolved in a small amount of distilled water and dialyzed against running tap water for 48 hours.

After dialysis for 48 hours the contents of the cellophane sacks were filtered to remove the euglobulin precipitate which was always present. The filtrate was adjusted to pH 5.3 with approximately normal lactic acid and the mixture was allowed to stand in the refrigerator overnight. On the following day it was filtered. The precipitate was redissolved in 0.1% sodium chloride and lyophilized in weighed bottles. The filtrate, or portions of it, were usually also lyophilized. When used in quantitative experiments, the dried material was redissolved in sufficient amounts of 0.9% sodium chloride solution to give a concentration of total solids of 12%.

Experimental. In order to study thrombic activity quantitatively, 1:10 or 1:100 dilutions were made from the sodium chloride solutions prepared to contain 12% total solids. Citrated normal human plasma was used as a source of fibrinogen. One milliliter of plasma was pipetted into each of a series of beakers and diluted with 30 ml. of 0.9% sodium chloride solution. Varying amounts of diluted pseudoglobulin preparations were added, and the amount of precipitated fibrin was determined. The fibrinogen content of the plasma was also determined by a modification of Cullen and Van Slyke's method of recalcification.[1]

When the standard procedure for preparing rabbit pseudoglobulin was applied to beef plasma without isoelectric precipitation, it was found that the amounts of material required to convert fibrinogen to fibrin in normal human plasma contained much higher nitrogen concentrations than in those experiments in which rabbit pseudoglobulin was used. In order to eliminate the large amount of inactive nitrogenous material apparently present in the beef preparation, two isoelectric precipitations at pH 5.3 were done. Both filtrates and both precipitates were found to possess some thrombic activity. The second precipitation increased the activity only very slightly and decreased the yield of thrombic material considerably. After one isoelectric precipitation a material is obtained which is

usually as potent in promoting blood coagulation as rabbit thrombin without any isoelectric purification.

Table 1 shows a typical comparison of rabbit globulin with beef globulin prepared in the same manner and with beef globulin isoelectrically precipitated at pH 5.3.

TABLE 1.—COMPARISON OF RABBIT GLOBULIN WITH BEEF GLOBULIN

Source of thrombin	Mg. thrombin nitrogen added to 1 ml. plasma	Mg. fibrin precipitated
Rabbit plasma standard procedure	0.01	1.54
	0.02	1.89
	0.03	2.25
Beef plasma standard procedure	0.11	1.10
	0.21	2.40
	0.32	2.22
	0.53	2.50
Beef plasma after isoelectric precipitation	0.007	1.79
	0.01	3.07
	0.07	3.42

Two samples of swine plasma were treated in the same manner as that described for beef plasma, and materials were obtained possessing similar thrombic activity. Table 2 shows a comparison of these two preparations with one made from rabbit plasma.

TABLE 2.—COMPARISON OF RABBIT GLOBULIN WITH SWINE GLOBULIN

Source of thrombin	Mg. thrombin nitrogen added to 1 ml. plasma	Mg. fibrin precipitated
Rabbit plasma standard procedure	0.01	1.91
	0.03	2.61
	0.07	2.77
Oxalated swine plasma after isoelectric precipitation	0.01	1.54
	0.02	2.38
	0.05	2.78
Citrated swine plasma after isoelectric precipitation	0.006	2.76
	0.01	3.57
	0.02	3.73

The pseudoglobulin fraction of Parfentjev was also prepared from human plasma. The pseudoglobulin obtained was thrombic in nature, but the potency of the preparation in relation to precipitation of fibrinogen was much less than similar preparations from rabbits, swine or steer plasma. A typical assay is shown in Table 3.

TABLE 3.—POTENCY OF HUMAN THROMBIN

Source of thrombin	Mg. thrombin added to 1 ml. plasma	Mg. fibrinogen precipitated
Human plasma	0.05	0.63
	0.10	1.30
	0.20	1.54

Parfentjev[3] in his original procedure conducted the salting-out at a temperature of 37° C. or at room temperature. Because of the possibility of denaturation of proteins at these temperatures, it seemed of interest to investigate the effects of low temperatures on

the reaction. Therefore, one preparation of beef pseudoglobulin was made at about 4° C. The material obtained possessed thrombic activity similar to that of those beef preparations in which ammonium sulphate precipitation was carried out at 37° C. (Table 4).

The origin of thrombic activity derived from calcium-free plasma remains obscure, but some observations directed at a solution of this problem may be reported at this time.

Since a relationship between blood platelets and blood coagulation has been suggested for many years, an investigation was made of the thrombic activity of pseudoglobulin fractions prepared from beef plasma from which platelets had been removed. Berkefeld filtration and centrifugation were both used as methods of removing platelets. Two preparations were made on beef plasma after it had been passed through a Berkefeld filter. One of these possessed no thrombic activity, and the other was only slightly active (Table 4).

Two samples of beef plasma were then centrifugalized in an angle head centrifuge at 4200 r.p.m. to remove platelets, and the resulting plasma used for preparations of pseudoglobulin. In 1 instance the platelets were reduced from 128,000 to 8000 per c.mm. The final product possessed only slight thrombic activity. The second sample was centrifugalized after the addition of ether-phenol preservative. The platelets in this preparation were reduced from 26,000 to 6000 per c.mm. The final product was one of the most potent preparations made from beef plasma (Table 4).

Recent observations in this laboratory[4] show that after the addition of certain organic solvents to plasma a globulin may be isoelectrically precipitated which will coagulate oxalated plasma. In consideration of this finding, it seemed possible that ether and phenol used primarily merely as a preservative might actually be important factors in the production of thrombic activity. Moreover, in one experiment cited above, it was observed that plasma made poor in platelets after the addition of phenol and ether was very active, whereas removal of platelets before the addition of these substances apparently decreased the thrombic activity. To further investigate the effects of the ether-phenol preservative, one preparation of beef pseudoglobulin was made from which the preservative was omitted. The resulting material was of only fair potency as shown in Table 4. However, both the preparations made from swine plasma were without preservative of any kind, and both of these were very similar in thrombic activity to the most potent beef pseudoglobulins. As swine plasma was never used in this laboratory with phenol and ether, no comparison can be made for that species.

If calcium ions were present as an impurity during the preparation of the pseudoglobulin fraction, it is conceivable that reaction with the thromboplastin and prothrombin of the plasma might occur resulting in thrombic activity. In order to eliminate calcium ions

from the reaction, one preparation of beef pseudoglobulin was made in which the saline was heavily oxalated at each step of the procedure, as shown in Table 4. The material thus prepared possessed some thrombic activity, but was much less active than those made by the standard procedure.

Table 4 presents the results obtained when preparations made with the variations described above were tested with normal human plasma.

TABLE 4.—VARIATIONS IN PREPARATION OF BEEF PSEUDOGLOBULIN TESTED WITH NORMAL HUMAN PLASMA

Modifications in preparation	Mg. thrombin nitrogen added to 1 ml. plasma	Mg. fibrin precipitated
Beef plasma standard procedure	0.007	2.22
	0.014	2.92
	0.028	3.39
	0.070	3.62
Temperature 4° C.	0.007	0.35
	0.014	2.21
	0.028	2.62
	0.070	2.88
Berkefeld plasma, Experiment I	0.52	2.45
	1.04	2.84
	2.08	3.12
Berkefeld plasma, Experiment II	4.36	0.00
Platelets removed by centrifugation	1.83	1.29
	3.65	1.85
Platelets removed by centrifugation after phenol-ether	0.008	2.00
	0.016	2.69
	0.031	3.06
	0.079	3.15
Ether-phenol omitted	0.11	0.54
	0.21	2.28
	0.53	2.43
Calcium ion excluded	0.13	1.47
	0.26	2.53
	0.65	3.15

Discussion. When beef plasma and swine plasma are used as sources of a globulin fraction possessing thrombic activity, other nitrogen-containing fractions not effective in the coagulation of blood are present in larger amounts than in similar material prepared from rabbit plasma. Therefore, purification by isoelectric precipitation is necessary in order to obtain material possessing thrombic concentration equal to that of rabbit pseudoglobulin.

Apparently it is unnecessary to keep plasma at 37° C. during precipitation with ammonium sulphate. When the procedure was carried out in a refrigerator or in running tap water at about 4° C., the globulin fraction prepared possessed approximately the same amount of thrombic activity as those samples prepared at 37° C. It seems probable that the method could be simplified by carrying it out at room temperature without loss of thrombic activity.

An attempt to investigate the relationship between platelets and the thrombic activity of beef pseudoglobulin indicates that the

platelets may play an important rôle. Table 4 shows that with pseudoglobulin prepared from Berkefeld or centrifuged plasma, nearly 100 times as much "thrombin" nitrogen was required to precipitate fibrin from normal human plasma as was necessary when platelets were present in normal amounts. In fact, one sample of Berkefeld plasma was completely inactive even when the nitrogen content of the pseudoglobulin used was several hundred times as great as that usually required. It is, of course, difficult to determine whether it is the removal of platelets alone by Berkefeld filtration which reduces the potency or whether other necessary factors are also removed.

When phenol and ether were added to plasma before centrifuging to remove platelets, an active clotting globulin was obtained, as shown in Table 4. The explanation of this might be that the platelets had already been affected by the ether and phenol before centrifuging so that the necessary part of the platelets was in solution despite the fact that a count showed very few platelets to be present.

As further evidence of the reaction of ether and phenol, it may be seen from Table 4 that when no preservative was used, more than 10 times the usual amount of "thrombin" nitrogen was required to precipitate fibrin.

In the one experiment in which oxalated saline was used to eliminate calcium ions as a reagent impurity during the preparation, material of reduced thrombic activity was produced. Table 4 shows that roughly 10 times as much nitrogen was needed in the samples of this particular pseudoglobulin preparation as in the standard samples in order to precipitate equal amounts of fibrin.

Summary. 1. Beef plasma and swine plasma may be used as sources of a pseudoglobulin possessing thrombic activity similar to that in rabbit plasma. The beef and swine preparations require more purification in order to obtain activity equal to that derived from rabbit plasma.

2. In the preparation of a beef globulin fraction possessing thrombic activity, the fractionation of proteins with ammonium sulphate may be carried out between 4° and 37° C.

3. The thrombic activity of beef pseudoglobulin is diminished in plasma which has been passed through a Berkefeld filter or made poor in platelets by rapid centrifugalization unless ether and phenol have been added previously to the plasma.

4. Ether and phenol, used originally only as a preservative, appear to play some part in the formation of thrombic activity of beef pseudoglobulin, although potent material has been prepared from swine plasma without this preservative.

5. When oxalate is added to exclude the possible effect of calcium ions on the preparation of beef pseudoglobulin, a material is obtained which possesses diminished thrombic activity.

6. Human plasma when treated by Parfentjev's procedure yields a pseudoglobulin having the properties of thrombin. The two samples of plasma used in this study did not produce as active a product as either rabbit, swine or beef plasma.

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EXPERIMENTAL RIBOFLAVIN DEFICIENCY IN MAN

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Following the original descriptions of the syndrome of riboflavin deficiency in man by Sebrell and Butler,[8] and its experimental duplication by them,[9] Kruse, Sydenstricker, Sebrell, and Cleckley[6] demonstrated the occurrence of superficial keratitis in riboflavin deficiency. Their findings were similar in many respects to the ocular changes in riboflavin-deficient animals described by Bessey and Wolbach,[1] and Eckhardt and Johnson.[4] Further work by the original investigators has served to confirm their earlier observations and has led to their conclusion that "at the present time it seems that superficial vascular keratitis is the earliest and most common visible manifestation of riboflavin deficiency as well as a rather reliable index of early deficiency of the B group of vitamins."[4]

The work of these investigators is of fundamental importance, suggesting as it does a clinical method of some precision in the diagnosis of deficiency disease.

It seemed to us important, therefore, to determine if possible the time relationships in the development of this clinical sign. Accordingly the following experiment was undertaken.

Methods. Since 1939 the Students' Health Service of the University of Minnesota has provided a diet table for the benefit of

those students requiring dietary management for any cause, chiefly obesity, diabetes mellitus, and peptic ulcer. A detailed description of its operation has been published elsewhere.[2] From the group receiving their meals at this diet table, 6 volunteers, 1 male and 5 females, were chosen for this study. Their status prior to the experimental period may be tabulated as follows:

TABLE 1.—STATUS OF VOLUNTEERS

Name	Sex	Age	Reason for prior dietary treatment	% of standard weight	Duration of prior dietary treatment (days)
L. M.	M	23	Obesity	137	79
M. B.	F	18	Obesity	135	147
F. D.	F	29	Obesity	143	95
E. L.	F	25	Obesity	134	15
J. G.	F	18	Obesity	127	82
J. H.	F	19	Obesity	133	91

All of these individuals had been treated for the periods noted above by a reduction diet calculated to contain the following:

TABLE 2.—COMPOSITION OF REDUCTION DIET

Calories	1013
Protein	70 gm.
Fat	37 gm.
Carbohydrate	100 gm.
Calcium	0 96 gm.
Phosphorus	1 46 gm.
Iron	0 015 gm.
Vitamin A	4500 I.U.
Thiamine	1 6 mg.
Ascorbic acid	80 mg.
Riboflavin	2 1 mg.

Since all of these individuals had demonstrated a satisfactory rate of weight-loss prior to the experimental period, it was hoped that their coöperation in the experimental régime would be good.

These 6 volunteers were divided into 2 groups of 3, designated as "control," and "experimental." All were begun on a diet calculated to contain the following:

TABLE 3.—COMPOSITION OF EXPERIMENTAL LOW RIBOFLAVIN DIET

Calories	1300
Protein	71 gm.
Fat	62 2 gm.
Carbohydrate	160 9 gm.
Vitamin A	4140 I.U.
Thiamine	1 24 mg.
Ascorbic acid	96 mg.
Riboflavin	471 μg.

Three daily menus were used in rotation. These are listed in Table 4.

All riboflavin values of foods were taken from the tables of Bowes and Church.[3]

TABLE 4.—MENUS OF EXPERIMENTAL LOW RIBOFLAVIN DIET

Day 1	Riboflavin (μg.)
1300 Calories	
BREAKFAST:	
3 oz. grapejuice + 4 tbsp. gelatin	9
Applesauce	33
White bread (not enriched)	15
Butter (½ pat)	1
Bacon (fried—3 str.)	15
Coffee	
	73
LUNCH:	
Spaghetti and tomatoes with 25 gm. ground meat	36 20
Grapefruit section salad with 1 inner leaf lettuce	35 4
White bread (not enriched)	15
Butter (½ pat)	1
Crushed pineapple	25
Tea or coffee	
	136
DINNER:	
Beef tenderloin	130
Carrots	20
Small boiled potato	40
50 gm. tomato salad with 1 inner leaf lettuce	20 4
½ white bread (not enriched)	15
Butter (½ pat)	1
Sliced banana	10
Coffee or tea	
	240
Total micrograms riboflavin, 449	

Day 2	Riboflavin (μg.)
1300 Calories	
BREAKFAST:	
3 oz. pineapple juice + 4 tbsp. gelatin	18
Tangerine	25
Bacon (3 str.)	15
White bread	15
Butter (½ pat)	1
Coffee	
	74
LUNCH:	
Vegetable soup	55
1 oz. boiled ham (sandwich)	35
2 white bread (thin) (cut crust)	30
Butter (½ pat) lettuce leaf	5
Baked apple	30
Tea or coffee	
	155
DINNER:	
Beef roast	130
Asparagus (canned)	35
Small baked potato	40
50 gm. lettuce salad (inner leaves)	20
White roll	15
Butter (½ pat)	1
½ grapefruit	35
Coffee or tea	
	276
Total micrograms riboflavin, 505	

Day 3	Riboflavin (μg.)
1300 Calories	
BREAKFAST:	
3 oz. grapefruit juice + 4 tbsp. gelatin	18
Sliced banana	10
Bacon (3 str.)	15
White bread	15
Butter (½ pat)	1
Coffee	
	59
LUNCH:	
Rice with tomatoes	35
3 str. bacon	15
50 raw carrot strips	10
White bread	15
Butter (½ pat)	1
Red apple	30
Coffee or tea	
	106
DINNER:	
Cured ham (75 gm.)	150
Baked or boiled potato	40
Stewed tomatoes	45
Celery salad (50 gm. with inner lettuce leaf)	27
½ white bread	15
Butter (½ pat)	1
Canned blueberries	15
Coffee or tea	
	293
Total micrograms riboflavin, 458	

In addition to this diet, all 6 received daily vitamin and mineral supplements as follows:

TABLE 5.—VITAMIN AND MINERAL SUPPLEMENTS

Calcium	1 gm.
Phosphorus	1 gm.
Iron	.2 gm.
Nicotinic acid	50 mg.
Calcium panthothenate	2 mg.
Pyridoxine	2 mg.

In addition to these, the control group received without their knowledge a daily supplement of 3 mg. of riboflavin. Two of us (J.J.B. and C.E.S.) who followed the physical status of these volunteers throughout the experiment, were unaware of the identities of the individuals in the control and experimental groups until the end of the experiment.

Each volunteer was requested to report for slitlamp study at the beginning of the period, and twice a week thereafter. (Later once a week.)

Because of the exigencies of the school year, this experiment had to be terminated, unfortunately, after only 5 weeks of observation.

Results. *Experimental Group.*

1. *M.B.* Developed aphthous stomatitis 21st-28th days. No objective evidence of glossitis. No diffuse soreness of mouth or tongue. No eye symptoms at any time. Stated that the diet was very unpleasant, and admitted extra-food intake on numerous occasions. Gained 5 pounds.
   Slitlamp findings:
   Day 1: Negative. Day 7: Negative. Day 15: Negative. Day 22: Slight fullness of vessels in upper nasal quadrants. Day 29: No change. Conclusion: No abnormalities demonstrated.
2. *E.L.* Developed aphthous stomatitis 35th day. No diffuse soreness of mouth or tongue; no objective manifestations of glossitis. On 14th day developed photophobia which persisted until resumption of normal diet. Weight loss 8½ poynds.
   Slitlamp findings:
   Day 1: Negative. Day 6: Negative. Day 13: Possibly slight increase in amount of blood in limbal plexus. Day 20: No change. Day 27: No change. Day 35: No change. Conclusion: No abnormalities demonstrated.
3. *J.H.* Complained of unusual fatigue beginning on 8th day. Disappeared 6 days after resumption of normal diet. No eye symptoms at any time. No glossitis. Weight gain 4 pounds.
   Slitlamp findings:
   Day 1: Negative. Day 5: Negative. Day 10: Negative. Day 15: Negative. Day 22: Negative. Day 29: Negative. Conclusion: No abnormalities demonstrated.

Control Group.

1. *L.M.* Complained of visual fatigue after 7th day. Also noted general fatigue after 7th day. Weight loss 12 pounds.
   Slitlamp findings:
   Day 1: Negative. Day 8: Negative. Day 15: Negative. Day 22: Few streamers off nasal limbus, left eye. Day 29: Additional fine capillary extension from nasal limbus, both eyes. No secondary capillary loops.
   (On Day 30 L.M. resumed a "normal" diet.)
   Day 51: No change.
   (On Day 52 L.M. was given 9 mg. of riboflavin a day in addition to his "normal" diet.)
   Day 65: No change. Riboflavin discontinued.
   Day 105: No change. Fine capillary streamers still present. Still complains of occasional eye fatigue. (No uncorrected refractive error.) Weight gain of 8 pounds since discontinuance of experimental diet. Conclusion: Minimal, but definite abnormality demonstrated.
2. *F.D.* No symptoms of any kind. Weight loss 2 pounds.
   Slitlamp findings:
   Day 1: Negative. Day 5: Negative. Day 12: Negative. Day 19: Negative. Day 26: Negative. Conclusion: No abnormalities demonstrated.
3. *J.G.* Sore tongue from 21st to 25th day. No objective signs. No visual symptoms. Weight loss 1 pound.
   Slitlamp findings:
   Day 1: Negative. Day 5- Negative. Day 17: Negative. Day 24: Negative. Day 31: Negative. Conclusion: No abnormalities demonstrated.

Comment. The failure of our experimental subjects to develop corneal vascularization is not in accordance with the statement of Sydenstricker, Kelly, and Weaver,[13] who state, "Under experimental conditions, within a few days, often only two, empty capillaries can be seen arising from the apices of the loops outlining the scleral projections . . . . in 2 or 3 days more they form complete loops through which red cells circulate irregularly and in clumps." Their experimental conditions were not cited. We are not prepared at present to say that this lack of agreement is of any significance. The conditions of our experiment did not permit us to be certain of the coöperation of our subjects. Further, we have no objective evidence (*i. e.*, diminished urinary excretion of riboflavin) that our subjects were actually deficient in riboflavin. It may be that a longer period of deprivation is necessary to bring an individual on a previously adequate intake of riboflavin to the point where objective signs are manifest. Repetition of this experiment with coincident determination of urinary riboflavin is obviously indicated, and will be initiated in the near future.

The significant point, it seems to us, which emerges from this study is the fact that definite evidence of corneal vascularization occurred in one of the subjects of the *control* group, in spite of an intake of riboflavin of approximately 3.5 mg. per day, whereas an intake of approximately 2.1 mg. of riboflavin per day for 79 days previously, while on the reduction diet, had not resulted in keratitis. This previous period would seem to eliminate defective absorption or defective phosphorylation of riboflavin as etiologic factors in the keratitis.

Further, a "normal" (non-reduction) diet for 3 weeks following the experimental period failed to alter the keratitis, as did the administration of 9 mg. of riboflavin a day for 14 additional days. Theoretically, there are several possibilities which might account for the appearance and persistence of keratitis in a patient whose intake of riboflavin conformed to present ideas of adequate riboflavin supply, and which was greater than a previous known intake of riboflavin.

Summary and Conclusions. 1. Superficial keratitis, like cheilosis,[7] may be found to be a relatively non-specific response to vitamin deficiency.

2. Lack of "balance" in vitamin intake may cause riboflavin deficiency, even with a relatively high intake of riboflavin. Sydenstricker,[11] and Spies, Stanberry, Williams, Jukes, and Babcock[10] have emphasized the rôles of pyridoxine and pantothenic acid, respectively, in the mobilization and utilization of riboflavin. Unfortunately, presently available food analyses are not complete enough to permit us to compare pyridoxine and pantothenic acid intakes of our reduction and experimental diets.

3. It may be that riboflavin *plus* other dietary factors are required

to prevent keratitis. In this connection it may be recalled that Johnson and Eckhardt have already suggested that "factors additional to riboflavin are concerned with the healthy state of the cornea".[5] And Sydenstricker, Sebrell, Cleckley, and Kruse[14] stated: "It seems possible that other conditioning factors as yet undetermined, may be potent in the production of ariboflavinosis."

4. The keratitis in case L.M. may have been coincident, and unrelated to vitamin deficiency. This is supported by its failure to subside after large doses of riboflavin, plus a "normal" diet.

5. Superficial keratitis, of the type described as specific for riboflavin deficiency, appeared in a patient on a known and theoretically optimal intake of riboflavin. This failed to disappear on a "normal" diet, plus additional riboflavin.

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FOCAL NECROSIS OF THE ADRENAL CORTEX

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In reviewing the literature on focal necrosis of the adrenal cortex, it is seen that a wide variety of etiologic factors are implicated. Moschcowitz[4] reported 2 cases, and offered a résumé of pathologic and experimental observations. One of his cases was a 41 year old male who died of uremia complicating calculous disease of the kidneys. He observed more than a dozen foci of necrosis in the adrenal cortex, with intense surrounding polynuclear reaction.

The periadrenal tissue was hemorrhagic with thrombosis of the veins. The second case was that of an 8 year old girl with chronic glomerulonephritis. Multiple focal necrosis with polynuclear reaction were seen, in addition to bacterial emboli in the regional vessels. The relationship of the bacterial emboli to the foci of necrosis is open to question. His illustrations show a notable absence of reaction about some of the bacteria-filled vessels, and the presumption remains that postmortem bacterial proliferation may be represented. His conclusions took cognizance of this, for he inferred that adrenal cortical necrosis may result from either vascular or "toxic" effects. Moschcowitz quoted many authors, including Ziegler, Aschoff, Neusser and Wiesel, Loper and Oppenheim, and Roux and Yersin, all of whom stressed the rôle of infectious diseases in the causation of focal necrosis of the adrenal cortex. Diphtheria was associated with the necrotic lesions most often, but similar lesions were noted in cases of variola, typhoid and tetanus. Experimentally induced lesions were noted particularly with diptheria toxin. However, identical changes were produced with *B. tetani*, *B. anthracis*, and the pneumococcus. McLaughlin noted the common association of focal necrosis of the adrenal cortex and Curling ulcers of the duodenum in cases of fatal burns. He quoted Weiskotten, who reported 6 cases of fatal burns showing hemorrhage and necrosis of the adrenal. McLaughlin inferred a definite bearing of the adrenal necrosis upon the causation of the Curling ulcers and succeeded in producing ulcerations of the duodenum and elsewhere by experimental destruction of the adrenal.

Hass[2] reported a case of a premature infant with multiple areas of focal necrosis with inflammatory reaction in the liver and adrenal. He noted acidophilic and basophilic intranuclear inclusion bodies in the parenchymal cells and suggested a virus etiology. Grollman[1] summarizes the subject of focal necrosis by the following statement: "In acute bacterial toxemias, focal necrosis are often seen in the *zona faciculata* which resemble those occurring in the spleen and other viscera." Oestern[5] reported a case of miliary necrosis in the lung and adrenal in a premature infant who died on the second day of life. He noted the resemblance of the necrotic foci to tubercles, and described a polynuclear inflammatory reaction. In arriving at a conclusion as to the etiology of the necrosis, Oestern quoted the work of several authors including Kaufmann, Amsler, Schneider, Schwartz, and Konschegg. Most of these writers stressed focal necrosis of the liver in infants in their discussion of etiology. Plump "U" or "S" shaped rods stained by the Levaditi method, and not by Gram stain; Gram-positive rods resembling diphtheroids; and complete absence of bacterial agents were reported by different authors. Oestern, Kaufmann, and Amsler were uncertain of the etiologic agent, but suggested "intestinal intoxication" as a possible mechanism.

TABLE 1.—RÉSUMÉ OF 18 CASES OF FOCAL NECROSIS OF THE ADRENALS

Case	Age	Sex	Cause of death	Infectious disease process	Endocrine disturbances	Associated pathologic changes
1	64	F	Hypertensive heart disease	.....	.....	Thrombosis of pulmonary arteries with infarction of lung; thrombosis of veins of thorax and pampiniform plexus
2	63	M	Pulmonary embolus	Fibrinous pericarditis	Diabetes mellitus	Thrombophlebitis of right thigh
3	33	F	Meningococcus meningitis	Meningitis	.....	Thrombosis of cerebral veins
4	62	F	Lobar pneumonia	Pneumonia	.....	
5	54	F	Generalized peritonitis	Peritonitis (strep. non-hem.)	.....	Carcinoma of cervix with ulceration and fistula formation to peritoneum, ulcerative colitis and proctitis (post-radiation); thrombosis of pulmonary vessels
6	63	F	Cholemia	Terminal sepsis (*B. coli*)	Diabetes mellitus	Carcinoma of gall bladder with obstructive jaundice, miniature abscesses of kidney; pulmonary artery thrombosis with infarction
7	25	M	Generalized peritonitis; sepsis	Peritonitis (*B. coli*) (strep. non-hem.)	.....	Suppurative appendicitis
8	23	M	Diabetic coma	.....	Diabetes mellitus	
9	54	M	Hodgkin's disease	Terminal sepsis	.....	Miniature abscesses of liver and spleen
10	56	M	Neuroblastoma	Lobar pneumonia (pneu. Type XVI)	.....	Metastasis in adrenal
11	48	F	Cerebral hemorrhage	.....	Diabetes mellitus; basophilic adenoma of pituitary	Cushing's syndrome, obesity, hirsutism, hypertension, diabetes
12	44	F	Uremia	.....	Eosinophilic adenoma of pituitary	Malignant nephrosclerosis; hyperplasia of parathyroids; dissecting aneurysm of aorta; pancreatic fibrosis
13	84	F	Coronary thrombosis; myocardial infarction	Lobular pneumonia	Diabetes mellitus	
14	14 mos.	F	Massive bronchopneumonia	Bronchopneumonia	.....	Congenital stenosis of duodenum with intestinal obstruction; dilatation of pancreatic ducts; chronic intestinal pancreatitis; terminal intussusception of ileum with infarction; leukoplakia of esophagus
15	68	F	Bronchopneumonia	Bronchopneumonia; membranous cystitis, pelvic peritonitis	.....	Pernicious anemia ?
16	75	F	Multiple peritoneal abscesses	Peritoneal abscesses; bronchopneumonia	.....	Thrombosis of left uterine vein; thrombosis of splenic artery; cachexia
17	35	M	Brain abscess	Brain abscess; meningitis (strep. hem.)	.....	Multiple recent peptic ulcers; traumatic softening of pituitary (operative)
18	76	F	Shock, multiple fractures	.....	.....	Multiple fractures; acute ulceration of jejunum

The 18 cases of focal necrosis of the adrenal cortex listed below in Table 1 represent lesions discovered incidentally during the routine 3080 autopsies at the Queens General Hospital in the first 6 years of its existence. With the exception of Case 16, all lesions were seen microscopically in the single section of the adrenal gland taken in all autopsies. In Table 1 are listed all relevant associated clinical and pathologic findings. During the course of the analysis of these cases, the presence of other factors such as blood sugar and urea levels, blood pressure, and focal necrosis in other viscera was noted. Since there was no correlation of these factors with the finding of adrenal necrosis, they are not listed. All lesions were studied on formalin fixed, paraffin imbedded material stained with hematoxylin and eosin. Giemsa and Gram stains were done on lesions showing recent changes.

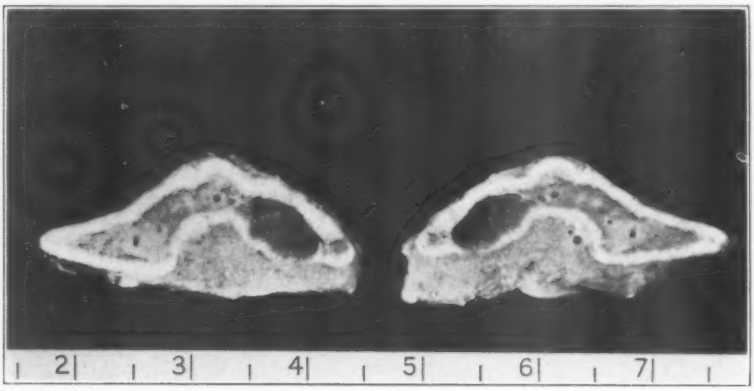

FIG. 1.—Case 16. Oval dark brown nodular cytonecrotic mass in reticularis zone. (× 2.5.)

Age and Sex. Eleven females and 6 males comprise the series. The ages range from 14 months to 84 years, with a mean age of 50 years.

Pathologic Features. The single gross lesion measured 8 by 2 mm. (Fig. 1). It appeared as an elliptical, translucent, brownish mass situated in the reticularis layer, and was raised slightly above the surface of the adjacent parenchyma.

The histologic features are outlined in Table 2. The lesions were of recent origin in 12 instances and showed evidence of chronicity in 5. The acute changes were of 2 types. The first consisted of a focal coagulation necrosis of the adrenal cortical tissue. The size of such areas varied greatly, ranging from 25μ to 2340μ. They were encountered mainly in the *zona fasciculata*, but were also seen in the other 2 layers and in one instance reached to the capsule (Fig. 2). Some of the zones of necrosis bore a distinct resemblance to tubercle

structures. Complete autopsy examination in these cases failed to reveal any active or inactive tuberculosis and stains for acid-fast bacilli were negative. In Case 1, the necrotic focus simulated a miniature caseous tubercle, while in Case 17 a central area of coagulation necrosis was surrounded by a ring of lymphocytic cells and a single Langhans giant cell. The giant cell may have been of the foreign body type (Fig. 3), reactive to the liberation of lipoid material in the region of the necrotic focus, though fusion of altered cortical epithelium is suggested by cytology and staining properties.

TABLE 2.—RÉSUMÉ OF HISTOPATHOLOGIC FINDINGS

Case No.	Size in μ	Location	Histopathologic features
1	195	Fasciculata	Focal coagulation necrosis; resemblance to caseous tubercle; multiple foci (3)
2	?	Reticularis	Numerous areas of rounded calcification and fibrosis along reticularis with no reaction
3	520	Glomerulosa and outer fasciculata	Focal collagenous scarring; rather thin remaining glomerulosa
4	390	Fasciculata (inner)	Focal coagulation necrosis with atrophy of adjacent cells and some brownish pigmentation
5	156	Fasciculata (inner)	Focal coagulation necrosis of group of cells; little inflammatory reaction
6	25 to ?	Reticularis, fasciculata	Multiple focal rounded and linear areas of cytonecrosis with and without pigmentation
7	1500	All 3 layers	Focal coagulation necrosis with marked inflammatory reaction, polynuclear cells predominating; adjacent atrophic degenerated cortical cells
8	?	Reticularis	Multiple focal areas of calcification in rounded globules; wide triangular zone of fibrosis adjacent to medulla
9	780	Fasciculata (mid-zone)	Focal coagulation necrosis with vacuolization of regional cortical cells; preservation of sinusoidal and endothelial structures
10	150	Fasciculata	Focal coagulation necrosis with included fibrinoid material with surrounding acute inflammatory reaction
11	260	Fasciculata (upper)	Localized rounded fibrotic zone with some hyalinosis and ossification
12	400	Reticularis (inner)	Rounded zone of fibrosis
13	2340	Fasciculata, glomerulosa and capsule	Focal coagulation necrosis without atrophy of cells; marked regional inflammatory reaction and adjacent zone of liposis
14	450	All 3 layers	Multiple areas of focal coagulation necrosis with regional polynuclear reaction
15	580	Interrenal tissue	Centrally placed extensive coagulation necrosis without inflammatory reaction; no change in adrenal
16	8 x 2 mm.	Reticularis	Pigmented degenerated and atrophic necrotic cells in nodular adenomatoid area
17	720	Glomerulosa, fasciculata	Focal coagulation necrosis with distinct tubercle-like structure, regional Langhans type giant cell and considerable round cell infiltration locally and in medulla
18	50–70	Fasciculata	Multiple with both focal coagulative zones and zones with marked involutional atrophic changes

In the center of one of the foci of coagulation necrosis (Case 10), fibrinoid material was identified. The amount of inflammatory reaction around the areas of coagulation necrosis varied greatly, and was usually polynuclear in character. In Case 15, in which the necrosis occurred in an island of interrenal cortical tissue, no inflammatory cells could be seen (Fig. 4). In Case 14, the marked polynuclear exudation approached the reaction seen in suppurative inflammation (Fig. 5). Hemorrhage in the necrotic foci was an inconstant feature, but was definite in some cases and is of theoretical interest. Although the basic structure of the adrenal cortex was destroyed in most of the necrotic foci, distinct preservation of

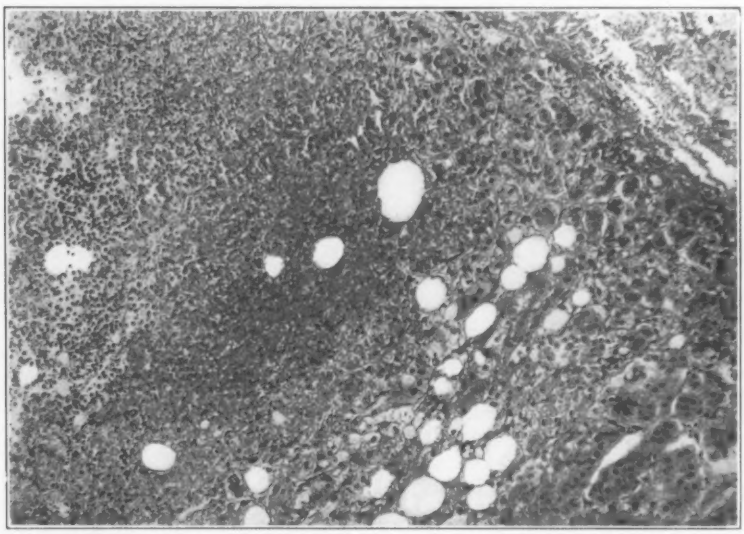

FIG. 2.—Case 13. Area of coagulation necrosis with surrounding polynuclear reaction adjacent to zone of liposis. Extension of inflammatory exudate to region of capsule seen at upper right. (× 175.)

sinusoidal reticulum and endothelium was seen in Case 7 (Fig. 6). This type of coagulation necrosis was sharply delimited without transition to regional cortex.

The other type of acute change was one of localized cytonecrosis of a varying number of individual cortical cells (Fig. 7). The nuclei of the cells were for the most part pyknotic, but occasionally could not be seen at all. The size of such cells was almost invariably smaller than usual. The cytoplasm was coarsely granular and often contained abundant brownish pigment which made the entire necrotic focus stand out in sharp contrast against the regional normal parenchyma. It was this feature which undoubtedly accounted for the ease with which the gross lesion shown in Figure 1

made itself evident. The necrotic pigmented cells often appeared shrunken and separated from the basement membrane. This type of focus showed greater tendency to transition to regional cortical epithelium with degenerative changes in adjacent cells. No thrombosis was found in the smaller or larger vessels of the tissue adjacent to any necrotic zones.

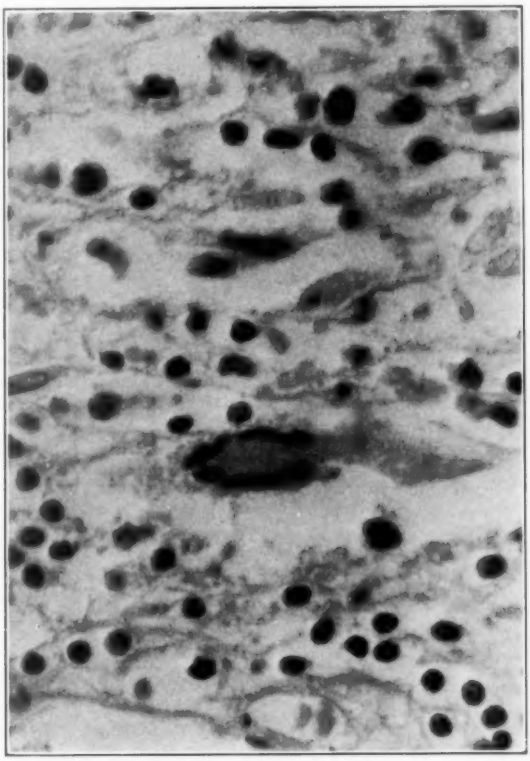

FIG. 3.—Case 17. Langhans type of giant cell and round cell infiltration adjacent to area of coagulation necrosis resembling caseous tubercle beyond upper border of photograph. (× 750.)

Numerous stages in the organization and eventual fate of the necrotic foci were observed. One early phase of the organization process was seen in Case 12. A well-rounded zone was seen in which the center was composed of finely fibrillar collagenous tissue, with small round inflammatory cells and somewhat dilated capillary channels containing red blood cells (Fig. 8). In Case 3, more coarsely fibrillar collagenous tissue was seen with included fibroblastic cells and no inflammatory cells (Fig. 9). The scar tissue in this instance extended into the regional cortex and capsule in an

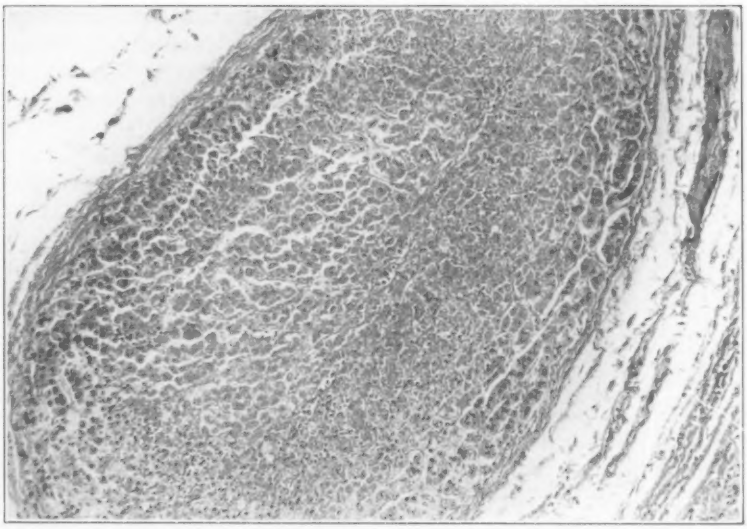

FIG. 4.—Case 15. Interrenal tissue showing extensive central coagulation necrosis with peripheral rim of intact cortical tissue. Note pyknotic nuclear remnants in left lower portion. Capsule of adrenal seen at lower right margin. (× 175.)

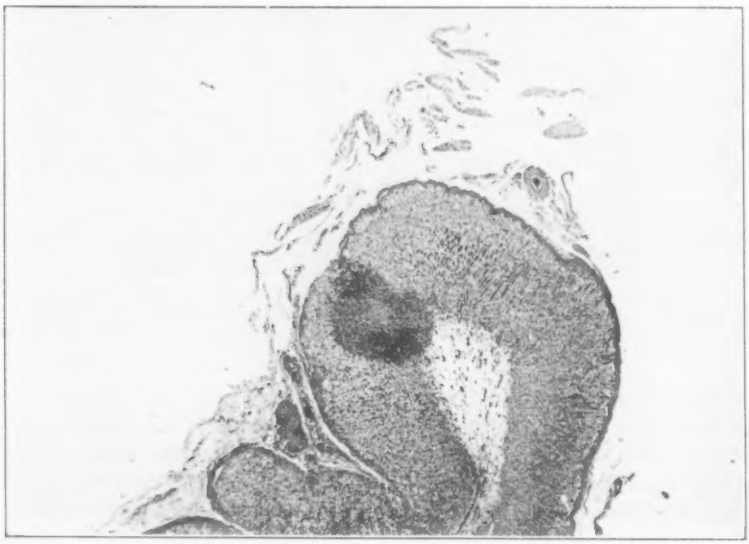

FIG. 5.—Case 14. One of several rounded foci of coagulation necrosis with marked polynuclear reaction at periphery in a 14 month old infant with remnant of organized atrophic centrally placed androgenic zone. (× 24.)

irregular manner. Diffuse and focal calcification of groups of cortical cell remnants both within and separated from large fibrotic areas was also noted in Cases 2 and 8. In Case 11, a rounded hyalinized fibrotic zone was present, with a central area of ossification and early marrow formation (Fig. 10).

Discussion. In the literature, focal necrosis of the adrenal has been associated with actual infection or "toxic" states. Eleven of our 12 cases showing recent changes had some infectious disease

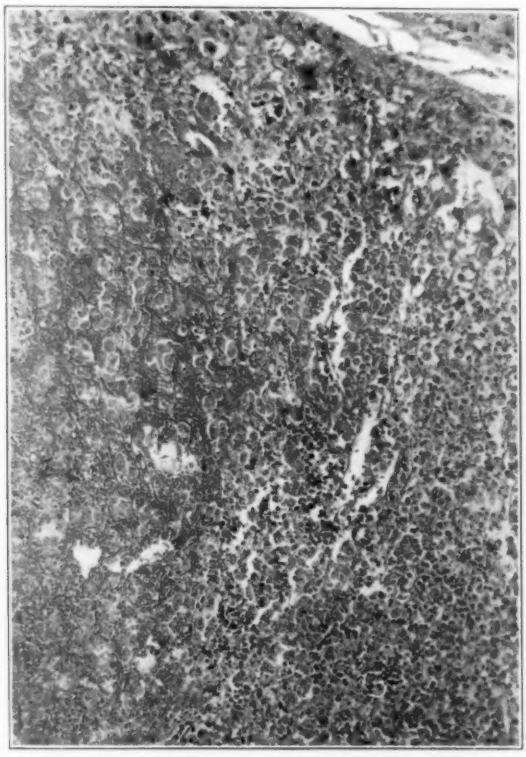

FIG. 6.—Case 7. Zone of coagulation necrosis of cortical cells with preservation of reticular structure and adjacent polynuclear reaction. (× 175.)

process, varying from limited lobular pneumonia to extensive suppurative peritonitis. It is our impression that endocrine abnormalities do contribute in some measure to the evolution of focal necrosis. Diabetes mellitus was noted in 5 of the cases, and it is important to note further that no infectious process was present in 2 of them. In one of the latter, Cushing's syndrome was fully developed, and the diagnosis of basophilic adenoma of the pituitary was confirmed at autopsy. In the other instance, an eosinophilic

adenoma of the pituitary was noted as an incidental finding in a case of malignant nephrosclerosis with uremia. Two of the cases included above with the infectious processes, showed cachexia. Arterial and venous thrombosis in widely divergent locations outside of the adrenal was noted in 6 cases. In only one instance, a case of hypertensive heart disease, neither an infectious process nor an endocrine problem was present.

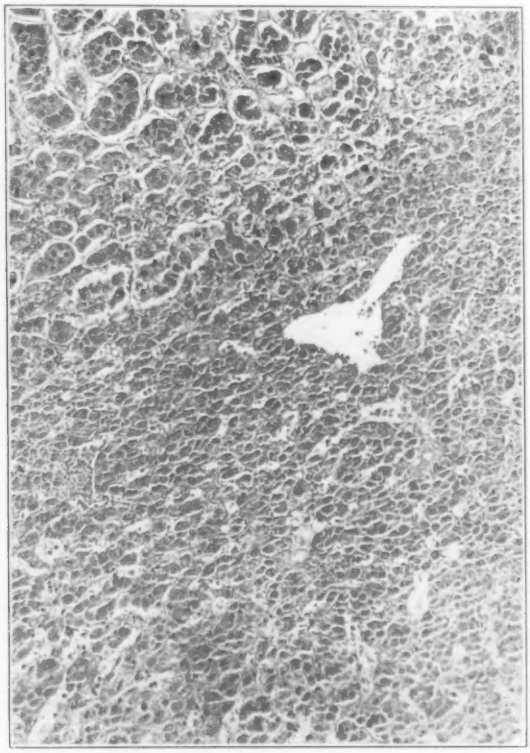

FIG. 7.—Case 16. Microscopic section corresponding to gross lesion seen in Figure 1. Edge of large zone of cytonecrosis. (× 175.)

The multiplicity of factors observed above favors the consideration that focal adrenal cortical necrosis is not a specific disease entity with a single etiology, and tends to implicate a physiologic component in the reaction.

The possibility does remain that absorption of many necrotic zones occur. In the cases where the reticulum remains preserved, the preëxisting events of degeneration and necrosis may be completely lost to observation by regeneration of persistent cortical cells. The physiologic sequence of events is then approached.

With absorption, fatty replacement by large fat cells may produce the phenomenon of liposis occasionally seen in the adrenal cortex (Fig. 1).

The relationship of "exhaustion lipoidosis" of the fasciculata and the exaggerated physiologic involutional and degenerative changes in the reticularis zone, to the focal degenerative and necrotic foci described, is yet to be established. In the fully formed adrenal, the reticularis represents the final zone of degeneration and involu-

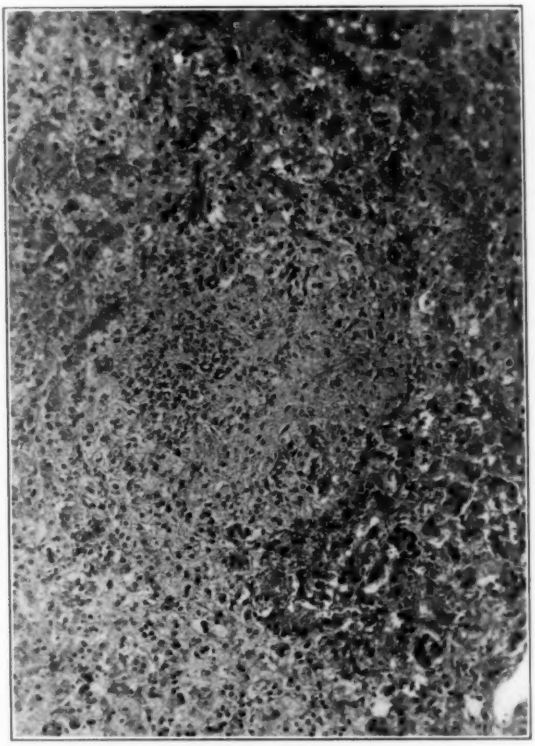

FIG. 8.—Case 12. Rounded nodular organizing zone. Note vascularization, round cell infiltration and fine fibrillar collagen. (× 175.)

tion. Usually the cells in the reticularis are more deeply stained, often showing brownish pigmentation due to lipochrome, with a more intense and compact eosinophilic staining of the cytoplasm, pyknosis of the nucleus, and general shrinkage and atrophy. In some of the focal zones showing progressive cytonecrosis, identical retrogressive changes were noted. At the periphery of centrally placed areas of coagulation necrosis, similar involutional changes were often seen in cortical cells. One gains the impression that the cyto-

necrotic areas described may actually represent exaggerated involutional phenomena normally noted in the reticularis. In like manner the foci of frank coagulative necrosis suggest an acute sudden response on the part of the cortical cells of an exaggerated nature and somewhat functional significance. It should be emphasized at this point that only cases which illustrated foci of actual necrosis of coagulative type or of progressive cytonecrosis of cells were included in this series. Foci of degeneration and atrophy seen within reticularis or other layers of the cortex, without necrosis, were excluded from consideration.

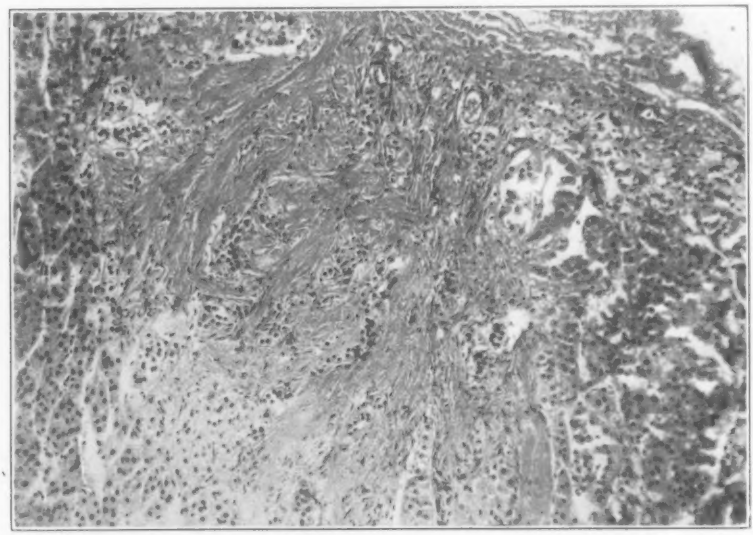

FIG. 9.—Case 3. Larger area of fibrous scarring extending from capsule in upper portion of field through glomerulosa and fasciculata. Note coarse fibrillar collagen. × 175.)

The phenomenon of focal necrosis in a solid parenchymal organ such as the liver has often been observed. Some have been established to be bacterial in origin, as in typhoid. Necrotic foci of identical nature have been seen in a compact endocrine organ like the pituitary gland. Such foci of necrosis, both in the pituitary and the adrenal vary in size. Complete necrosis of the pituitary giving rise to dramatic endocrine syndromes occurs especially associated with pregnancy. It is conceivable that areas of focal necrosis of the adrenal cortex may increase in size, merge and otherwise involve an extensive area sufficient to cause clinical symptoms of adrenal insufficiency. The presence of parallel degenerative and necrotic changes in a case of Addison's disease studied in this laboratory, associated with widespread fibrosis of the cortex acquires significance

on this basis. The atrophy and fibrosis repeated the changes noted above in the zones of focal necrosis undergoing organization. In several of the focal areas studied, intense congestion of the sinusoids and hemorrhage was found limited to the areas of necrosis and the immediate vicinity. In one instance fibrinoid material was found in the center of a lesion. Such findings represent a replica in miniature of the adrenal changes seen in the Waterhouse-Friedrichsen syndrome.

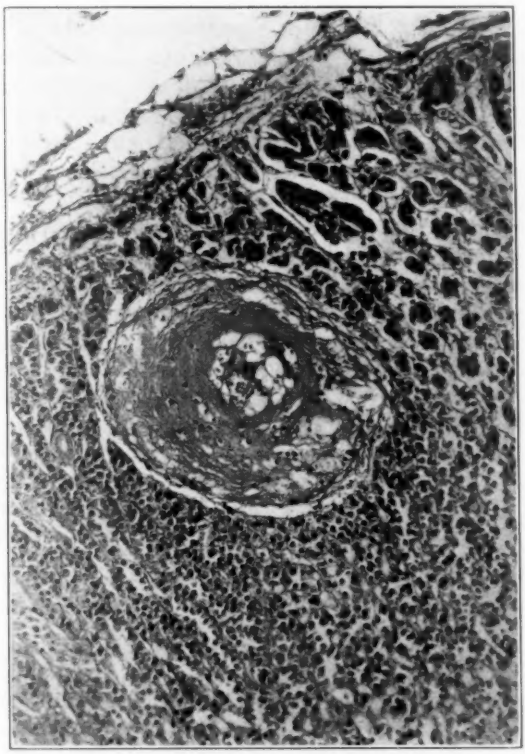

FIG. 10.—Case 11. Sharply delimited zone of hyalinized fibrotic and ossified area with beginning central marrow formation. (× 175.)

The findings of these small areas of focal necrosis of the adrenal cortex has no clinical application at present. It may be significant, however, in providing illustrative material for the basic mechanism operative in those widespread necrotic lesions giving rise to dramatic syndromes. In Case 18, a condition of profound shock following trauma was associated with focal necrosis of the adrenal and active acute ulcerations of the duodenum. This parallels the findings of McLaughlin for such a correlation. There also exists the possible

significance of the summation of recurring focal lesions in producing a progressive insufficiency or predisposing to a subsequent severe acute episode. Quite theoretical is the consideration of allergic sensitization to such specific cortical tissue with subsequent hypergic reaction.

The gradation in size of the foci of physiologic and degenerative changes and the small areas of focal necrosis, to the widespread diffuse lesions with established clinical syndromes suggests that attention might well be focussed on establishing a relationship or common denominator between the two.

Giemsa stains and Gram preparations on most of the acute necrotic lesions failed to demonstrate virus inclusions on bacteria *in situ*.

Summary. 1. Eighteen cases of focal necrosis of the adrenal cortex are presented.

2. The literature is reviewed and the etiologic factors of infection, toxemia, endocrine factors, and allergy, discussed.

3. A physiologic component in the production of the necrotic lesions is indicated by the multiplicity of etiologic factors, the apparent significance of endocrine states, and the gradation of such lesions in size and nature with involutional physiologic changes in the adrenal, and the negative bacteriologic and virus findings.

4. The possible significance and the relationship of such lesions to Addison's disease and to Waterhouse-Friedrichsen syndrome and to intestinal ulceration is intimated.

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A PLATELET–RED CELL CONJUGATION PHENOMENON AND ITS RELATION TO BLOOD COAGULATION

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The blood platelets have been studied very extensively but in most of the studies reported in the literature it has generally been considered that they carry out their mission in the coagulation process as individual agents. Very few observers have linked the function of the platelets to other formed elements in the blood.

The purpose of this paper is to call attention to a conjugation

phenomenon between the blood platelets and the red cells in normal blood, and to discuss the significance of this relationship in the light of the more recent knowledge of blood coagulation.

Hayem,[8] in 1889, studying fresh preparations of shed blood, noted that the red blood cells frequently fragment when included in a mass of degenerating platelets. Tait,[14] in 1918, in studies on clotting frogs' blood, described a property of the blood cells which manifests itself by red cells and platelets adhering to one another. He calls this "selective adhesion," and states: "When a film of frogs' blood clots, a course network of fibrin-like material is formed. Each node in this network consists of either a mass or a single thrombocyte around which the erythrocytes arrange themselves in rosettes. Not all the erythrocytes are involved, but only those lying in the vicinity of the thrombocytes. That portion of the involved erythrocyte which lies in immediate contact with the thrombocyte becomes constricted as if with a purse string . . . . the skin of the erythrocyte apparently adheres to the thrombocyte." This phenomenon is not an accidental occurrence but a deliberate "selective adhesion" only between the red cells and platelets, for he goes on to state: "On the other hand I have seen a granular leukocyte crawl from a distance to such a mass of thrombocytes and pursue its course over and past them, being in no wise impeded by contact with them."

This phenomenon may readily be observed in normal freshly shed human blood, both in dried stained smears and in moist preparations. When such specimens are examined under the oil-immersion lens, one can observe that where the platelets lie in contact with red cells, the red cells usually have become deformed. The extent of the red cell deformities run the gamut from that of slight indentation to complete division or actual fragmentation. Careful focusing further reveals that the contours of these deformities conform closely to the shape of the adjacent platelets, and that the edges of the deformed areas are rough and ragged, in contrast to the smooth unaffected edge of the rest of the red cell (Fig. 1).

Conforming to Tait's[14] observations in frogs' blood, not all of the human red cells are involved and the phenomenon is strictly a selective one, taking place only between the red cells and platelets (Fig. 2).

If a small drop of freshly shed normal human blood is placed on a slide, allowed to remain undisturbed for about 1 minute and then spread by dropping a coverslip over it, the red cell platelet conjugation can readily be observed. In such a preparation, clumps and masses of platelets can be seen which have one or more deformed red cells enmeshed among them.

In these wet preparations one can readily note the absolute selectivity of the phenomenon, for the leukocytes can be seen either at rest among the red cells or floating past them, but never becoming involved in the process.

The Effect of Anticoagulants. *Sodium Citrate.* When smears are made from both citrated and unmodified samples of the same blood, the citrated smears show a striking difference in the red cell platelet conjugation when compared to the unmodified smears. The smears of citrated blood show practically no deformed red cells, and the platelets for the most part lie freely in the spaces between the red cells. Only after diligent search can one find an occasional deformed red cell with its attached adjacent platelet (Fig. 3).

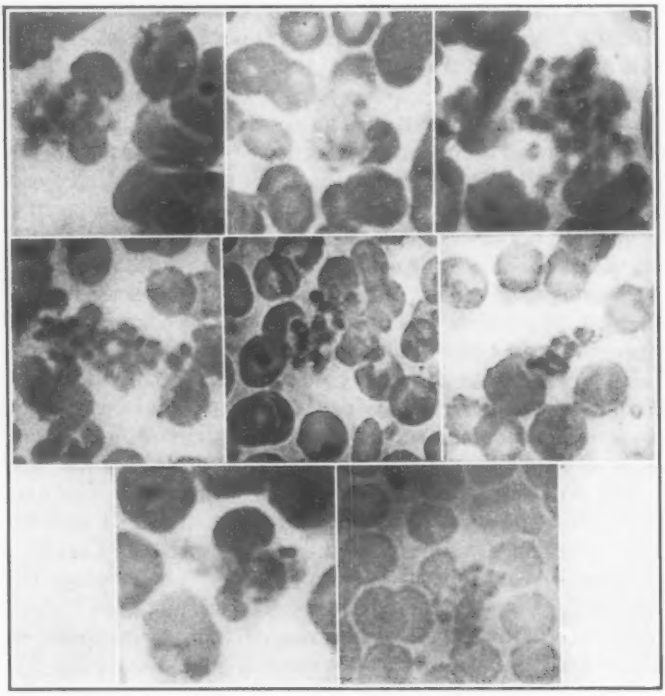

FIG. 1

Study of moist preparations of freshly citrated blood fails to show the presence of the agglomerations of platelets around enmeshed and deformed red cells, which are so readily seen in similar preparations of unmodified blood. The platelets are neither clumped nor attached to the red cells; few if any deformed red cells are seen; and the platelets individually and in small groups, lie about freely in the plasma between the red cells. It is interesting to note in this connection that Ferguson,[4] studying platelets under dark field illumination, found that in citrated plasma the platelets lose their "stickiness," but that when the plasma is recalcified, the platelets regain this stickiness and agglutinate in the usual manner.

Heparin, In Vitro. Fresh heparinized blood examined either in a dried stained smear or moist coverslip preparation also shows a marked diminution of the red cell platelet conjugation. In the moist preparations the platelets are not clumped around red cells, and in the dry smears practically no deformed red cells in conjunction with platelets can be seen.

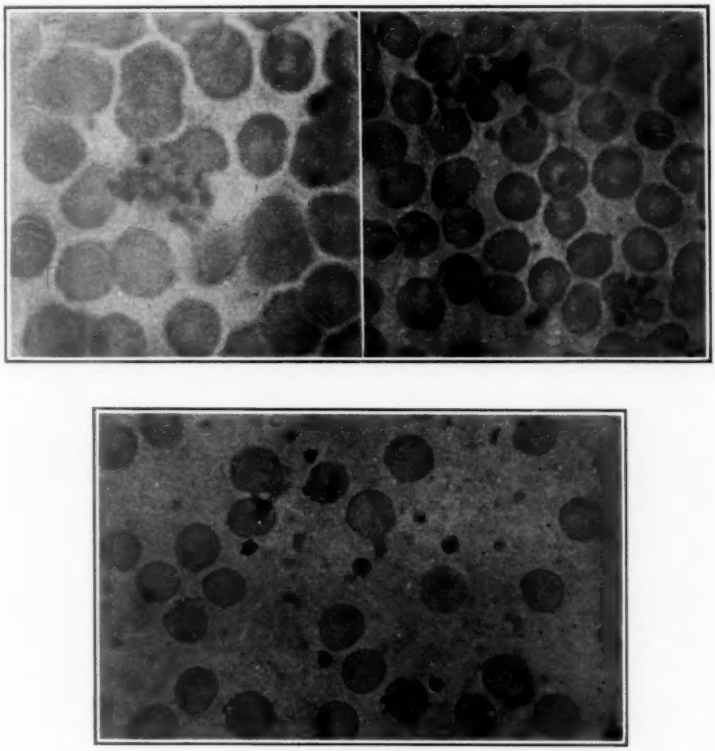

FIG. 2

Heparin, In Vivo. Stained smears and moist preparations of normal unmodified rabbit's blood show the red cell platelet conjugation to a greater degree than normal human blood. If, however, sufficient heparin solution is given intravenously to a rabbit to produce a prolongation of his coagulation time from the normal of about 4 minutes to over 24 hours, blood smears made during this period of prolonged coagulation show a marked diminution of the red cell-platelet conjugation. Although occasional deformed red cells with their adjacent platelets may still be found, they are scarce and the platelets generally are seen to lie freely in the areas between the red cells.

When the effect of the heparin has worn off and the rabbit's coagulation time has once again returned to normal, the red cell-platelet conjugation can again be observed to the normal degree in the blood smears and wet preparations.

Bleeding States. Blood from cases of thrombocytopenic purpura and hemophilia were studied because of the contrasting hematological defects in these two diseases. In thrombocytopenic purpura, while the platelets are greatly reduced in number, the coagulation time of the blood is fairly normal, while in hemophilia, although the platelets are normal in number, the coagulation time is usually prolonged. It was thought, therefore, that if the red cell platelet conjugation played some rôle in blood coagulation, it might become evident in a comparison of these two contrasting conditions.

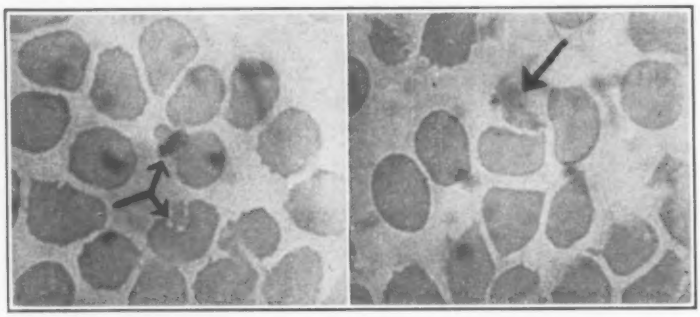

FIG. 3

Thrombocytopenic Purpura. Blood smears made from freshly shed unmodified blood in cases of thrombocytopenic purpura, often require prolonged and diligent search to find the few platelets which are present. However when they are found, they are almost without exception, seen to be in contact with one or more red cells, and these show the deformities previously described (Fig. 4).

In normal blood not more than perhaps 25% of the platelets seen in the smears are found in conjunction with deformed red cells, while in thrombocytopenic purpura, where a scarcity of platelets exists, 80% to 90% are found to bear this relationship to the red cells. In this disease, although the platelets are decreased in number, the red cell platelet conjugation is relatively increased rather than diminished to parallel the numerical reduction of the platelets.

Hemophilia. In cases of hemophilia, during periods when the coagulation time is markedly prolonged, and there have been no recent transfusions, blood smears as well as moist preparations consistently show marked diminution of the red cell platelet conjugation as compared to normal blood.

In the dried smears, the conjugation is not entirely absent, but

is encountered very infrequently as compared to normal blood. Here and there, in the hemophiliac blood smears one may find an occasional deformed red cell in contact with a platelet, but these are few in number. This diminution, although difficult to determine numerically, is nevertheless very apparent and the manner in which most of the platelets lie about in the spaces between the red cells is quite unlike their appearance in normal blood (Fig. 5).

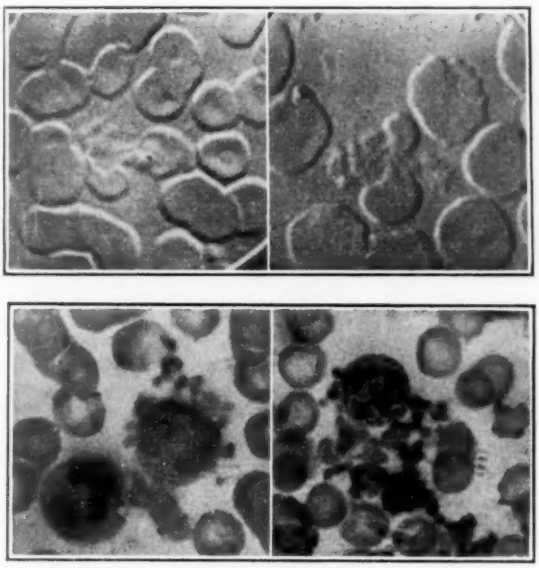

FIG. 4

Moist preparations of hemophiliac blood also show practically no red cell platelet conjugation. The platelets do not agglomerate around the red cells as they do in normal blood, but lie about singly or in small groups between the red cells in an innocuous manner. These moist preparations of hemophiliac blood resemble very closely those of citrated and heparinized blood described previously.

Discussion. Practically all the theories of normal blood coagulation, Morawitz,[12] Howell,[9] etc., accept the breakdown of the platelets and the consequent release of a ferment (thromboplastin—thrombokinase) as the earliest step in the coagulation process. The circumstances which induce the platelets to degenerate have been the subject of much and varied discussion in the literature. The most commonly accepted idea is the one suggested by Morawitz,[12] that when blood is shed the platelets come in contact with a water wettable surface and disintegrate, thrombokinase (thromboplastin) being freed in the process. The liberated thrombokinase

then acts as the trigger mechanism which sets off the complex series of chemical interactions, the end-result of which is clot formation.

Howell[10] states: "It would seem that in the circulating blood the content of thromboplastin must lie below the concentration required to induce prompt clotting. When blood is shed or withdrawn the content of thromboplastin is increased with some suddenness, by the mass disintegration of the platelets, to a concentration sufficient to cause clotting within a few minutes."

If, in order to degenerate rapidly and *en masse*, the platelets need to make contact with some surface, it appears that the blood, by employing the red cell platelet conjugation herein described, has at hand a constantly available mechanism of its own which fulfills such a requirement, without assuming the need for extraneous aid, such as Morawitz's[12] water wettable surface.

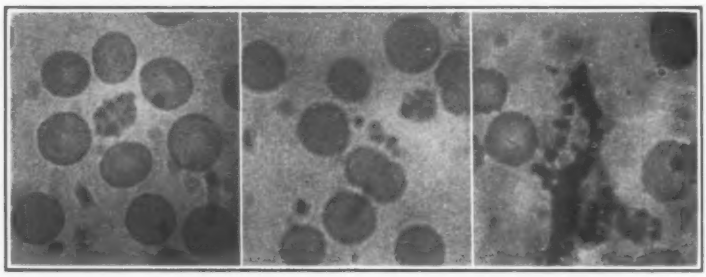

FIG. 5

It would seem that the platelets use the surfaces of the red cell for the physical contacts which they require in order to undergo rapid degeneration. The inability of blood to clot in the blood-vessels under normal conditions can be attributed to the motion of the blood preventing sufficient contact to permit conjugation.

Donahue and Howell[2] have shown that there is a destruction of platelets as the blood passes through the capillary areas of the systemic circulation. Since platelets and red cells come into intimate contact in the capillaries, it is possible that the destruction of platelets as noted by these authors results from the red cell platelet conjugation which occurs in the capillaries. The process is no doubt lessened by the fact that the blood flow in the capillaries, although sluggish, never becomes completely stagnant. The destruction of some platelets in the circulation is apparently the source of the minimal amounts of thromboplastin which are always found to be present.

When blood is shed and becomes completely stagnant, the platelet red cell conjugation, now unhampered by the blood flow, proceeds to such an extent that rapid mass degeneration of the platelets occurs. Under these conditions the quantity of thromboplastin

produced rises quickly to a concentration sufficiently high to set off the clotting process.[10]

Anticoagulants and Blood Dyscrasias. We may assume from their staining characteristics that the red cells, taking the acid stain, carry a negative charge, and the platelets, taking the alkaline stain, carry a positive charge. It is a fundamental law of physics that particles which carry opposite electric charges, when suspended in a liquid, are attracted to one another and when they collide their charges tend to become neutralized. If, as it is believed, the integrity and well-being of living cells depend on the maintenance of the electric charges which they normally carry, contact between the red cells and platelets with the consequent neutralization or loss of the platelet's normal charge may cause it to disintegrate very rapidly. In fact, changes in the electric charges of the platelets in clotting blood have actually been measured by Steuber and Lang.[11]

It seems logical to assume, therefore, that the anticoagulants, sodium citrate and heparin, which interfere with the red cell-platelet conjugation, do so because they disturb the electrolytic relationship which these formed elements normally maintain in relation to one another. Sodium citrate is, of course, an electrolyte, while evidence that heparin acts electrolytically is presented by Ferguson and Glazko,[5] who show that it functions like a polyvalent anion.

Studies on hemophiliac platelets by Howell,[10] Birch,[1] Quick[13] and Govaerts and Gratia[7] have demonstrated that while they remain in his own blood, the hemophiliac's platelets are "resistant" and do not disintegrate readily. However, when removed from hemophiliac blood, they lose this resistance to disintegration and behave exactly like platelets from normal blood. Further, Howell[10] has demonstrated that the only difference between normal and hemophiliac plasma is that the hemophiliac plasma contains less thromboplastin. This lowered level of thromboplastin is no doubt the direct result of the greater stability of the hemophiliac's platelets.

Since the defect in hemophilia appears to be the resistance to disintegration of the hemophiliac's platelets and since this resistance disappears when the platelets are removed from the hemophiliac's blood, one may assume that some factor present in normal blood which permits platelets to disintegrate is absent in hemophiliac blood. Because of the absence of this factor, the hemophiliac platelets, although they have the potentiality to disintegrate,[1,7,10,13] cannot do so.

In view of the ample amount of red cell-platelet conjugation in normally clotting blood and its striking diminution in hemophiliac blood, together with the fact that the hemophiliac platelets disintegrate normally when removed from the hemophiliac blood, one is confronted with the possibility that the red blood cells are an important and perhaps indispensable factor in the process which causes the breakdown of the platelets. The hemophiliac's red cells may

thus differ from the normal in that they lack some factor, the absence of which does not allow the red cell platelet conjugation to occur. In consequence the hemophiliac's platelets cannot disintegrate and thus appear to be resistant.

On this basis, it would only be necessary to make available normal red cells for the hemophiliac's platelets in order for them to undergo normal disintegration. Thus a transfusion of normal blood to a hemophiliac, supplying many normal red cells, may enable his platelets to disintegrate and reduce the coagulation time as well as help check the bleeding.

Two facts concerning the formed elements in circulating blood pointed out by Foster[6] in 1880, and Eberth and Schimmelbusch[3] in 1888, offer an explanation for the lack of intravascular clotting which might result from the red cell-platelet conjugation and its consequent platelet degeneration.

Foster[6] showed that "When fine particles of several kinds, some lighter than others, are driven through a narrow tube, the heavier particles flow in the axis and the lighter in the more peripheral portions of the stream." Later in 1888 Eberth and Schimmelbusch[3] showed that the formed elements of the blood, as they are propelled in the blood stream, arrange themselves similarly. The red cells form a central core, the leukocytes a concentric cylinder about the red cells and the platelets move along at the periphery of the stream nearest the vessel wall.

The dynamics of the circulation thus keeps the red cells and platelets apart until they reach the capillaries. Here they are forced into contact with one another, for the channels are so small that the cells pass through almost in single file. The electrolytic attraction of red cell and platelets also aids the mechanical forces in bringing about the red cell platelet conjugation in the capillaries.

The small amounts of thromboplastin formed from the disintegration of the platelets as a result of the red cell platelet conjugation in the capillaries, however, is not sufficient to produce intravascular clotting.

When normal blood is shed and lies completely stagnant, the behavior of the red cells and platelets is no longer controlled by the flow. The platelets and red cells, attracted now only by their opposite electric charges, gravitate unrestrainedly toward one another. The platelets being smaller, mass in clumps about the red cells, their electric charges become neutralized and they disintegrate *en masse*, liberating large amounts of thromboplastin. The amount of thromboplastin thus liberated is sufficient, in spite of the antiprothrombin present, to cause coagulation.

As previously demonstrated, the red cell-platelet conjugation is markedly diminished in the hemophiliac's blood, perhaps because of some defect in his red cells. Few platelets can thus degenerate in

his circulation and the lowered content of thromboplastin in his blood[6] may thus find explanation.

One cannot overlook the interesting possibility that the red cells which are involved in the conjugation are also destroyed along with the platelets. Hayem,[8] actually saw these red cells fragment when included in a mass of degenerating platelets.

Conclusions. 1. From the knowledge now available, in order for shed blood to clot, a sudden and massive disintegration of platelets appears to be necessary.

2. A conjugation phenomenon between platelets and red cells is described which is regarded as providing a means by which the platelets can employ the surfaces of the red cells for the contacts necessary to carry out this mass disintegration.

3. The reduction in platelets which normally occurs as the blood passes through the systemic capillaries may be due to a limited amount of red cell-platelet conjugation which takes place during the transit of the blood through the capillaries.

4. It is demonstrated that the anticoagulants, sodium citrate and heparin, interfere with the red cell-platelet conjugation.

5. The phenomenon is shown to be markedly reduced in hemophilia and relatively increased in thrombocytopenic purpura.

6. The fact that the hemophiliac's platelets have been shown to be normal in various ways would seem to indicate that the hemophiliac's red cells may be responsible for the diminished red cell-platelet conjugation in this disease.

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TUBERCULOSIS IN INDUSTRY*

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Tuberculosis has been a problem in industry for many years and from all available evidence is most likely to increase at the

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present time. Industry is now operating at its maximum and is, therefore, placing a greater strain on the worker than ever before. This increased strain will, without doubt, cause many breakdowns of those infected as well as many who are accepted into industry with latent or unhealed lesions. This increased hazard will result in lowering of productive output for the individual with the lesion and at the same time it will expose countless other workers to infection, and many will later succumb to the disease and thereby become progressively less productive.

There are thousands of workers entering industry today that would not have the same opportunity in more normal times. The high wages offered and the chance for independence will attract many workers, some of whom know they have tuberculosis but who are willing to take the chance with the hope that they will make the grade. There will be thousands of young women entering the factory and experience indicates that some will develop the disease as a matter of course. Their infection may occur inside or outside the plant but the continuous physical strain will lower their resistance permitting a tuberculous infection to develop into actual disease.

Workers today are moving from place to place in the country where jobs are available. Thus, those from low rate areas will go to areas with high tuberculosis rates and *vice versa*. In many instances housing will be inadequate causing congestion and, therefore, greater opportunities for the spread of infection not alone to the worker but to members of his family as well.

We are now entering an era of rationing of foodstuffs with a promise that more is to come, and as the war conditions continue we may expect to see a definitely lowered standard of living which is invariably associated with increases in tuberculosis. In the past, the existence of a state of war has always resulted in an increase in tuberculosis, and without doubt the situation today, which involves civilians almost as much as the armed forces, will bring greater strains on the civilian population than ever before. The successful outcome of this global conflict will depend as much on the output of industry as the tactical forces in the field. Therefore, those of us who must remain in civilian life must exert every possible effort to prevent further spread of infection in the community and this is a problem not alone of industry and its immediate workers but their families as well.

The spread of tuberculosis is conditioned in large part by the number of infectious cases in the community. The exposure of the worker to silica dust is the one agent of industry recognized to effect the susceptibility of the worker to tuberculosis. Other industrial agents have little, if any, effect on the individual insofar as tuberculosis is concerned. The problem of silicosis today is much less significant than formerly and, in addition, it is a problem

that can be very largely controlled through proper engineering procedures. Silica dust is limited to a few industries and, therefore, only a small percentage of all workers will ever be exposed to this extra risk. Thus, as important as silicosis may be as a clinical entity, or as a factor which increases susceptibility to tuberculosis, it constitutes but a small part of the problem of tuberculosis in industry.

Tuberculosis control programs have been developed by some of the larger industrial establishments in this country with great success. Many large industries have not developed such programs, and as a rule the thousands of small industries are without any program for the health of their employees. Selby[9] of the General Motors Corporation has stated that the purpose of industry is manufacturing and that to justify a medical service it must hold down the time lost by illness or injury. To quote him further, "So the over-all problem of tuberculosis control in industry is one of general community concern. It cannot be segregated within industry. . . . .

"So far as industry itself is concerned the sound long-range program is to clear the plant of tuberculosis and to keep it clear. This does not necessarily imply that all workmen who have tuberculosis are unemployable. It does mean that they must be employed only under conditions that permit them to work in safety to themselves and their fellow-employees and they must have close medical supervision."

The responsibility that may be assumed by industry in this matter is well illustrated by the program at the Michelin works in France.[10] The management of this company became interested in the tuberculosis problem early in this century. In 1915 they made allowances to families with a tuberculosis problem. By 1932 these allowances were made compulsory by law for all industries in France. In 1920 slum dwellings were torn down and replaced with model houses at modest rentals, and by 1932 all slum areas had been removed. In 1921 a dispensary was established for the tuberculous and pretuberculous by the Michelin Company. In 1922, 13% of new cases of tuberculosis were reported as in the advanced stages of the disease but by 1935 this percentage had fallen to 1.5%. Between 1931 and 1936 new cases reported fell from 181 or 8.2 to 84 or 3.8 per 1000 of the population.

There are a number of large industrial establishments in this country which grant special privileges to their employees who fall ill with tuberculosis, but none who also assume the complete family problem.

In New York City since 1933 the Department of Health has conducted an aggressive case-finding program among the apparently healthy adult population in selected groups.[2] In 1939, the first surveys were conducted in labor groups. The aim of these surveys

in industrial groups was to demonstrate the problem that existed and find a reasonable method for the conduct of routine surveys. It was hoped, once the problem was known and a method for its solution presented, that the worker and management might be brought together and establish a routine service. We have demonstrated in a number of surveys the prevalence of disease,[1,3,4] but we have not been able to induce labor to set up a continuing program of its own nor to induce labor to join with management in a program for tuberculosis control. This failure is, undoubtedly, the result of the distrust labor has of the attitude management might take in discharging men on the basis of the findings. It is, of course, possible to exaggerate many of the lesions that might be found in routine chest radiography, but it is believed, as indicated by Selby,[9] that in a joint program, adequate safeguards could be set-up that would protect the worker. If a laborer is suffering from an active or infectious tuberculosis, it is to his own advantage to seek proper care, and it is to the advantage of his companions to be protected from possible infection. The advantages to industry are obvious to all.

The surveys in labor groups in New York City have, therefore, been arranged entirely with labor organizations and never with management. Where cases have been found in need of care a way has always been found to induce the worker to accept treatment. Following some of our surveys the unions have contributed in excess of $10,000 in sick benefits and the payment for hospital care for their members.

The success of our program in various groups has been determined primarily by the interest and enthusiasm of the leaders of the union involved. Where this interest is dynamic the coöperation has reached as high as 70% of the union membership, and, conversely, where the union leaders were more concerned with routine union problems and treated the survey as a desirable but extra duty, the coöperation has been as low as 12%.

Between January, 1941, and up to July of 1942 a total of 15,644 individual members of 13 unions and 8 defense plants have been *x*-rayed and are reported here for the first time.

Of the above total, 10,168 were *x*-rayed in 1940 and 1941, and 5476 have been *x*-rayed in 1942 and are directly related to defense industries and two large commercial airlines. Some comment is necessary on the two groups as they were approached in a somewhat different manner. In the first group the unions involved for the most part approached the Department requesting a survey. Every effort was made to point out to the leaders of the various unions the estimated prevalence of disease expected, the importance of the survey, etc. Usually conferences were arranged with shop foremen to explain the program, the successful methods of approach in other surveys, and to answer any questions they might have. Then the

union by letter, posters and by word of mouth from the leaders and shop foremen endeavored to sell the idea to the rank and file of the membership. By and large in these surveys the percentage of cooperation was low compared to that in certain of the textile surveys previously reported, and it is believed that it was due primarily to the inability of the union leadership to put the program over, and to the fear of the worker that he might lose his job. In one of these unions (cooks and chefs) a strong appeal was made to them on the basis that if their membership could say that all were *x*-rayed and found free of tuberculosis there would result a decided economic gain to the membership, for they would then be offering a preferred worker to the trade.

In the defense workers surveys started in the early summer of 1942; the approach was made to them as a joint enterprise by the Department of Health using its WPA project, and the Queens Tuberculosis and Health Association. The latter organization served as a promotion agency by providing lectures, literature, posters and motion pictures, and in addition a worker to assist in making arrangements with union leaders and management. It is believed that such a combination of forces comprised an ideal method for utilizing the official and voluntary agencies resources to the best advantage. The Department of Health provided the technical services as in all other surveys.

At the outset, an attempt was made to secure the joint coöperation of labor and management in this program, because it was felt that such programs should become a routine for pre-employment as well as the regular periodic examination of employees. The first approach was made to labor leaders. As a result of preliminary discussions it became obvious that labor did not want to enter a joint program with management. Labor did not want management to be in the position of saying that they had given labor the service even though the entire program would be provided without cost to either. This was unfortunate because it later proved difficult in several instances to arrange for a set-up of the Roentgen ray unit in the shop where the service would have been more convenient to the worker and would, undoubtedly, have resulted in a much higher attendance. Even though union headquarters were located not far distant from the plant, there was evident a reluctance on the part of the men to come for Roentgen ray before or at the close of a shift.

This program is being continued and it is hoped that a joint effort by labor and management can ultimately be achieved.

Results of Surveys. The results of the first group of surveys are shown in Table 1. As these studies are made up of a number of different types of workers, some of which are small in number, they are being presented in less detail as compared to previous reports on surveys.[2] Instead of 5 year age divisions the mean age has been computed. By color, the material was predominantly white as

88.28% were so classified, 7.26% were negro, 4.16% Puerto Rican, and 0.3% unspecified. Approximately 80% of the individuals were males. Of the white, 80.75% were males. Of the negro, 65.72% were males; of the Puerto Rican, 74.7% were males, and of the others unspecified, 96.77% were males.

TABLE 1.—THE PREVALENCE OF TUBERCULOSIS BY ROENTGEN RAY EXAMINATION OF 10,168 UNION WORKERS IN NEW YORK CITY, 1940–1941

Type of population	Number x-rayed			Mean age	Number and per cent with tuberculosis					
					Active pul. tbc.*		Arrested		Primary	
	Total	M	F		No.	%	No.	%	No.	%
Food Trades	1,128	1,120	8	39.8	11	0.98	42	3.72	173	15.34
National Maritime Union	1,812	1,790	22	36.5	20	1.10	62	3.42	325	17.94
United Furniture Workers	421	395	26	30.9	4	0.95	7	1.66	63	14.96
Bleachers and Dyers	470	463	7	34.2	7	1.49	8	1.70	50	10.64
United Electrical Workers	1,108	1,051	57	33.1	4	0.36	22	1.99	101	9.12
Chain Restaurant Workers	1,127	883	244	42.2	5	0.44	48	4.26	218	19.34
Amalgamated Meat Workers	194	194	..	34.6	1	0.52	2	1.03	40	20.62
Laundry Workers	391	197	194	38.9	1	0.26	18	4.60	64	16.37
Dept. Store Joint Board	113	61	52	32.2	..	..	8	7.08	16	14.16
United Office and Proff. Workers	1,110	488	622	29.4	..	..	22	1.98	130	11.71
American Communications Assn.	564	330	234	30.5	2	0.61	16	2.84	72	12.77
Hat Block and Dyers	202	202	..	37.7	..	..	15	7.43	25	12.38
I. L. G. W. U. Needle Trades	1,528	906	622	29.0	14	0.92	38	2.49	126	8.25
Totals	10,168	8,080	2,088	34.5	69	0.68	308	3.03	1,403	13.80

* Active and clinically significant.

There were 69 cases of significant tuberculosis found in this entire group, 86.96% of which were in the white, 5.8% in the negro, 7.25% in the Puerto Rican and none in the unspecified groups. The white males accounted for 82.61% of all significant lesions in the entire group. Likewise, the 305 arrested pulmonary lesions were more prevalent in the white than other races. The percentage being 91.15%, in the negro 3.28%, in the Puerto Rican 5.57% and in the unspecified group 0.98%.

The 10,168 workers included in Table 1 represented 13 different union groups of widely varying types of occupation. There were 2449 members working in various food trades ranging from 0.19% to 0.98% of clinically significant tuberculosis.

There were 1812 members of the National Maritime Union with a prevalence of significant tuberculosis of 1.1%. The membership of this union is considerably larger than the numbers here reported, and from previous knowledge of the apparent frequency of tuberculosis among laborers of this class, it is believed that an even higher rate would be found among a more random sample.

The highest prevalence rate of significant pulmonary tuberculosis in this group, 1.49%, was found among members of the Bleachers and Dyers Union. On the other hand, it is interesting to note that they showed a much lower than average prevalence rate for chronic pulmonary tuberculosis (significant and arrested) and primary type lesions than for this group as a whole. There is no evidence to

suggest that this higher rate bears any direct relation to an occupational hazard in the industry. As the number of individuals reported here represents a substantial number of the entire membership, the results may, therefore, be considered as a fair sample of all workers.

It is of interest to note that no significant cases were found in the Department Store Joint Board members, though so small a number *x*-rayed is not a basis for any conclusion. The United Office and Professional Workers, predominantly females, revealed no active lesions. The Hat Bleachers and Dye Workers were small in number and showed no cases of significant tuberculosis. In each of the three foregoing groups a number of arrested cases were found.

The results of the examination of defense workers are shown in Table 2. The population in these surveys was made up almost exclusively of the white race. Thus, analysis by color is of no significance.

TABLE 2.—THE PREVALENCE OF TUBERCULOSIS BY ROENTGEN RAY EXAMINATION OF 5476 WORKERS IN INDUSTRIES DEVOTED TO DEFENSE ACTIVITIES IN NEW YORK CITY, 1942

Organization	Number *x*-rayed			Mean age	Number and per cent with tuberculosis lesions					
					Active*		Arrested		Primary	
	Total	M	F		No.	%	No.	%	No.	%
Fairchild Aviation Corp.	577	477	100	29.39	5	0.87	17	2.94	49	8.49
Premier Metal Company	290	199	91	31.40	1	0.34	8	2.76	29	10.0
Kollsman Instrument Company	1,484	1,051	433	29.80	8	0.54	40	2.7	137	9.23
American Seal Cap Corp.	188	87	101	28.51	3	1.6	4	2.13	16	8.51
Morey Machine Company	419	400	19	37.03	2	0.48	20	4.77	63	15.03
General Bronze Company	663	651	12	34.07	3	0.45	34	5.13	72	8.6
Pan American Airlines	615	475	140	25.19	2	0.33	5	0.81	44	7.15
American Airlines	1,240	999	241	26.35	3	0.24	21	1.69	132	10.65
Totals	5,476	4,339	1,137	29.57	27	0.49	149	2.72	542	9.9

* Active and clinically significant.

The division by sex in this group of workers is quite similar to that of the union workers in Table 1. This is, undoubtedly, caused by the preponderance of males in the Airlines, General Bronze Company and the Morey Machine Company. Of the two groups, the United Office and Professional Workers and the American Seal Cap employees were the only groups that had a preponderance of female workers.

There were 27 (0.49%) of the defense workers group that were classified as having significant pulmonary tuberculosis. The prevalence of arrested and primary lesions were also less than in the union workers in Table 1. The generally lower prevalence of disease may be in part a reflection of the lower average age of defense workers as compared to union workers. Also it may be presumed that the 1855 employees from airlines were selected for their work with greater care than in other industries. The prevalence rates in the

airline employees were 0.33% and 0.24%, which are the lowest rates for any of the groups in the two studies, excepting the Laundry Workers with 0.26%. It is not believed that a more representative sample of Laundry Workers would show so low a rate.

It was expected that silicosis might be found with some frequency in some of these industries. In the General Bronze Company there were 7 cases or slightly better than 1%. There were 2 cases in the employees of the Kollsman Instrument Company.

It is obvious, therefore, from this sample of defense workers that excessively high tuberculosis rates are not apparent. In fact, they are lower than for union employees regularly employed in commercial industries. Also they are lower than the prevalence rates found among draftees in New York City which have averaged about 1%. It should not be assumed from this study that the tuberculosis problem in defense industries as shown by this sample is of minor importance as the numbers involved are too small for such a conclusion.

Discussion. The findings in these studies are fairly typical of similar examinations by others and again confirm our previous observations that as a group the employed population invariably reveals less significant pulmonary tuberculosis than those unemployed and on relief. It is also obvious that the prevalence of tuberculosis varies considerably on the basis of occupation, but that so far as evidence is available there is no reason to believe that the occupations studied here can be considered as direct causative agents in tuberculosis.

It is of interest to point out the rather high prevalence of chronic pulmonary tuberculosis of an arrested type noted in the workers in these groups. These lesions, based on all acceptable criteria, are of long standing and for the most part give no evidence of potential danger in the future unless some untoward circumstances arise that will materially lower resistance. Further evidence of this fact has been found in our surveys which have frequently included repeated survey examinations of the same individual and that have shown no change in their lesions. This point has been emphasized in the studies of Sawyer[8] and Reid[7] in which they have followed such cases over varying periods of time.

The foregoing studies, as well as our own, indicate the need for sound clinical judgment in the evaluation of such lesions in pre-employment examinations as well as those found in surveys of industrial workers. It is well to remember that the lesion found at a given examination represents the accumulation of pathology over the years up to that time. The proper evaluation of such lesions will prevent the unnecessary hospitalization of many of these individuals or the exclusion of the individual from work. This policy has been followed in the handling of pre-employment as well as other types of studies by this Department with the result

that many individuals with lesions apparently arrested have been continued in their positions while periodic Roentgen rays confirm their stability. Also in our experience, it is found that approximately one-half of the lesions originally classified as significant on the survey radiograph will later be found to be arrested. In many of these lesions the individual is allowed to continue his regular activity during the period of supervision. The period and frequency of supervision varies according to the individual case and character of the lesion. These lesions are of decidedly more importance in the younger age groups, the females and colored.

Thus, if properly handled, these surveys of industrial workers need not jeopardize the job of the worker. On the other hand, if he does have an active tuberculosis, he should not expect to be allowed to continue in his job where he will be a potential source of danger to his fellow workers.

Reid[7] and Fellows[5,6] have reported extensively on the program at the Metropolitan Life Insurance Company. Their studies indicate that following the pre-employment examination and the annual reëxamination, new lesions will develop. The average incidence rate for the 10 year period, 1930 to 1939 inclusive, was 2.12 per 1000 males per year and 2.58 per 1000 females per year, the rate for females being the greatest between 20 and 24 years, and the rate for males exceeding the female peak but occurring at ages above 40 years. The periodic annual reëxamination has resulted in a steady decline in prevalence from 0.4 in 1930 to 0.1 in 1939. Fellows points out that there was no significant difference in the development rate of pulmonary tuberculosis in employees whose first roentgenogram was classified as negative when compared to a similar group whose first roentgenogram showed a healed primary. Both authors point out the increased prevalence of pulmonary tuberculosis among pre-employment groups as compared to regular employees. Undoubtedly, the routine supervision of employees detects lesion in their early stages and thereby prevents the development of advanced infectious cases.

Reid[7] reported on 139 pre-employment cases of apparently arrested chronic pulmonary tuberculosis at time of first roentgenogram and reëvaluated in 10 years. There was no conclusive evidence of reactivation during that time, though 1 case was so reported elsewhere but not confirmed, and another had an unstable lesion by Roentgen ray but no signs of symptoms or institutional supervision. Sawyer[8] indicates that in 75 arrested or inactive cases, that 16% of the minimals relapsed in from 1 to 5 or more years, whereas, 52% of the advanced cases relapsed. These cases were drawn from employees that cured for tuberculosis and later returned to work and, therefore, are not comparable with the cases found in pre-employment examination by Reid. As a result of the program conducted by Sawyer, there has been a reduction in the

morbidity rate from 2.08 in 1923 to 0.47 per 1000 in 1939. This is a greater reduction than was reported for the community at large in which his employees resided.

The studies presented here, as well as numerous other studies in the current literature, clearly indicate the prevalence of tuberculosis that may be found and the procedures by which such work can be done economically in industry. It is not meant to imply that a chest roentgenographic service is an entire medical program, but rather a part that should be supplemented by other sound medical procedures in determining physical disabilities among prospective, as well as regular employees.

The larger industries can set up programs similar to those of the Eastman Kodak Company in Rochester, the Metropolitan Life Insurance Company in New York City, General Motors Corporation in Detroit, and a host of others. These organizations have found that the investment pays dividends, as it results in less loss of time for illness and, therefore, increases the productiveness of the employee as a unit.

There is no reason why the smaller organizations may not combine resources to accomplish the same job. It is encouraging to note that the Federal agencies now interested in production for the war effort are giving increasing attention to the health and welfare of the worker in the shop as well as the home. As Selby has remarked, the responsibility for tuberculosis control does not rest alone with industry but must be paralleled by an active community program.

Summary. The results of findings in the roentgenographic examination of 15,644 union workers in various industries in New York City are analyzed.

There was found to be a prevalence rate of 0.61% with evidence of clinically significant pulmonary tuberculosis.

The prevalence of chronic pulmonary tuberculosis of apparent arrest was 2.92%. The prevalence of healed primary lesions for the entire group was 12.43%.

Surveys of this type are valuable in revealing the prevalence of chronic pulmonary tuberculosis and should be the basis for a definite program in medical care of the industrial employee. Such a service should provide pre-employment as well as periodic re-examination.

The handling of the pulmonary phase of such services requires competent clinicians trained in chest pathology, otherwise overemphasis may be placed on lesions of no importance as well as the reverse. If such work is properly handled, there is no reason to believe that the worker will be unjustly discriminated against because he presents a pulmonary lesion.

The increased tempo of industrial production, with all the varied social and economic problems attendant in these times, is justifi-

cation for the establishment of a tuberculosis control program in all industries. Such a program is greater than can be handled by the local Department of Health and is a responsibility that should be shared jointly by management and organized labor.

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ASPIRATED BONE MARROW STUDIES IN NORMAL MACACUS RHESUS MONKEYS.*

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This paper is published chiefly for investigators working with monkeys. The literature on the hematologic findings in monkeys, contains but few publications on peripheral blood, and none at all on the bone marrow picture of this animal.

The peripheral blood picture of the monkey has been discussed in some 24 publications, the most recent being published in 1938. Scarborough,[9] in an analysis of the published data, calls attention to the deficient study of many of the blood constituents.

According to Scarborough[9] the red blood cells in the monkey are biconcave discs, showing some variation in size. Rarity of abnormal forms is the rule, and polychromatophilia is moderately frequent. Hayem[3] failed to encounter nucleated cells in the peripheral blood of the monkey after studying 4 different species. Anderson and Neill[1] found but one nucleated cell in 10 monkeys studied. Krumbhaar[6] determined that the average of reticulocytes in monkey blood (Macacus) is around 0.3%, with a normal range of from 0 to

* This work was performed on *Macacus rhesus* monkeys living in Santiago Island Colony approaching the most natural of habitats for these animals. The island is located about 1 mile from the eastern coast of Puerto Rico, and the primate colony is maintained under the auspices of Columbia University.

0.8%, the reticulations being more delicate than in man or other animals. The size of the erythrocytes is equal to those of man, the average diameter being 7.1 micra (Hayem[3]).

The average number of total red blood cells reported by four authors,[1,3,7,13] and recapitulated by Scarborough,[9] is around 5,590,000 per cmm. with a normal range of 5,000,000 to 7,000,000. Krumbhaar and Musser[7] did not find influence of age or size of the animal upon the number of red blood cells.

Results from studies in 36 animals demonstrate that the hemoglobin estimation varies tremendously as put forth by three different authors.[1,5,7] Minima of 63, 73, 88 and 85% are reported; averages of 75, 67, 85, 103 and 95%, maximums from 82 to 115%. As these estimations were performed under widely different conditions and methods, a great variation is to be expected.

Krumbhaar and Musser[7] described the polymorphonuclear neutrophils as having as many as 10 to 15 lobules in their nuclei, and the lymphocytes, as being larger than in man. Lucas and Prizer[8] found that it was difficult to differentiate the large lymphocytes from the monocytes. The total number of leukocytes as reported by nine investigators[1,3,4,7,8,11,12,13] average 16,210 per cmm. (range 8000 to 25,000), the average differential findings being:

	%	Range
Polymorphonuclears	42.2	30–50
Lymphocytes	52.8	40–60
Large mononuclears or transitionals	1.5	1–12
Eosinophils	3.7	1–5
Basophils	.32	.1–.5

The average count of platelets in the peripheral blood stream of the monkey, as reported by Krumbhaar and Musser,[7] is 267,000 per cmm., with a variation from 155,000 to 424,000.

As explained before, no comparison can be established in our bone marrow studies, since we have been unable to find citations in the literature in relation to this subject. In Table 3 we have added a comparison with normal human marrow (sectioned), as given by Custer and Krumbhaar.[2] They obviously have used different criteria for allocating nucleated red cells, polys and lymphocytes than those used in this study.

Materials and Methods. *Bone Marrow Studies.* Forty healthy Macacus rhesus monkeys were submitted to bone marrow aspirations; 21 were males and 19 females, with ages ranging from 6 months to 12 years, and weight oscillating between 1.5 and 11.5 kilos. There were 4 infants, 8 young and 28 adults.

The marrow was aspirated through an 18-gauge needle attached to a 20 cc. syringe, since strong negative pressure is needed to obtain even minute quantities of marrow. The animal was tied to a table, the head turned to one side, and the midsternum was cleaned up with iodine and alcohol. The needle was introduced in the midline, and the site of greater resistance was located in the sternum. Then the needle was screwed obliquely at an angle of 45° into the marrow cavity with very slight pressure.

TABLE 1.—BONE MARROW PICTURE OF MACACUS RHESUS MONKEYS, COMPARED WITH THE ADULT HUMAN.

	Infant monkeys (4).				Young monkeys (8).				Adult monkeys (28).				Normal human.	
	Range, %.		Average, %.		Range, %.		Average, %.		Range, %.		Average, %.		Average, %.	
Sternal Marrow.														
Megaloblasts	0–1.0	...	0.37	...	0–1.0	...	0.24	...	0–0.8	...	0.15	...	0.0	
Early erythroblasts	0–2.5	...	1.32	...	0–1.6	...	0.91	...	0–4.5	...	0.99	...	14.8	
Late erythroblasts	2.0–9.3	...	5.82	...	0.4–7.5	...	4.75	...	0.2–10.0	...	4.35	...		
Normoblasts	6.7–20.5	...	**12.3**	...	7.0–14.2	...	**10.79**	...	3.0–20.4	...	**10.30**	...	18.2	
Total (red cell series)	...	10.5–31.0	...	**19.82**	...	10.6–21.0	...	**16.69**	...	3.6–27.4	...	**15.80**	...	33.0
Myeloblasts	0–0	...	0	...	0–0.5	...	0.11	...	0–0.5	...	0.11	...	0.6	
Premyelocytes	0.5–0.7	...	0.5	...	0–1.0	...	0.6	...	0–5.6	...	1.18	...	9.0	
Neut. myelocytes	1.5–13.5	...	5.42	...	3.4–9.5	...	5.8	...	1.2–13.0	...	**4.25**	...	**34.6**	
Eos. myelocytes	0.5–1.0	...	0.67	...	0–2.4	...	0.62	...	0–1.5	...	0.33	...	2.0	
Bas. myelocytes	0–0.5	...	0.12	...	0–0	...	0	...	0–0.4	...	0.03	...	0.0	
Metamyelocytes	**4.5–6.0**	...	5.2	...	1.5–15.0	...	5.49	...	2.5–18.0	...	7.18	...	14.6	
Poly. neutrophils	**34.5–45.0**	...	**40.05**	...	37.6–49.5	...	**42.55**	...	25.0–60.5	...	**46.86**	...		
Poly. eosinophils	1.0–4.0	...	2.3	...	0–4.0	...	2.15	...	0–7.5	...	1.86	...	3.0	
Poly. basophils	0–0.3	...	0.2	...	0–0.5	...	0.17	...	0–1.2	...	0.08	...		
Total (granulocytic series)	...	43.0–67.5	...	**54.52**	...	50.2–70.2	...	**57.5**	...	40.0–78.2	...	**61.89**	...	63.8
Lymphocytes	12.0–33.3	...	**25.57**	...	8.6–34.0	...	**25.2**	...	5.8–47.2	...	**21.57**	...	0.0	
Monocytes	0–0	...	0	...	0–0.2	...	0.05	...	0–0.6	...	0.11	...	2.2	
Plasma cells	0–0.3	...	0.07	...	0–2.0	...	0.56	...	0–2.5	...	0.62	...	0.0	
Megakaryocytes	0–0	...	0	...	0–0	...	0	...	0–0.2	...	0.01	...	1.0	
Total	...	12.0–33.6	...	**25.65**	...	9.2–34.8	...	**25.81**	...	7.8–47.4	...	**22.31**	...	3.2

Aspiration at times was quite difficult, yielding marrow for only a few smears, due to the scarcity of the material and to its richness in fat. The sternum of the monkey is quite soft, and cartilaginous or soft bone is often traversed by the needle with no obtention of marrow. Thus, it is advisable to perforate the hardest portions of the bone that are usually encountered in the midsternum.

Smears of the marrow were made and studied after having been stained with the Jenner-Giemsa stain. Differential counts were performed in all the 40 bone marrow specimens; an average of 500 cells being counted in each.

Results. *Infant Monkeys.* In 4 infant Macacus rhesus monkeys, the bone marrow differential counts yielded the following results (see Table 1): The megaloblasts appeared to be scarce. The early erythroblasts ranged between 0 to 2.5% (average, 1.32%), while the late erythroblasts had a variation between 2 and 9.3% (average, 5.82%). The normoblasts were present in percentages between 6.1 and 20.5 (average, 12.3).

There were no myeloblasts in any of the samples of the infants' bone marrow and but few premyelocytes. There was an average of 5.2% metamyelocytes and 40.05% of adult neutrophils. Eosinophils and basophils were scarce.

The lymphocytes ranged between 12 and 33.3% in four samples, while plasma cells were rare.

Young Monkeys. The marrow of 8 young monkeys was studied (see Table 1). Megaloblasts showed about the same percentage as in the infants. Both early and late erythroblasts were slightly fewer than in the infant monkeys, while the normoblasts were fewer.

Myeloblasts were found in only two samples. The premyelocytes doubled the count in infants; the neutrophilic, eosinophilic and basophilic myelocytes were about the same. Metamyelocytes and adult polymorphonuclears averaged much the same as for the infants.

There were as many lymphocytes in the bone marrow of the infant as in the young animals; but we found some monocyte and plasma cells in the marrow of the young monkeys.

Adult Monkeys. We studied 28 adult Macacus rhesus monkeys in the same way as with infants and young (see Table 1). In this series all the elements of the red cell series were slightly less common than in the other two series.

Myeloblasts were still rare, but the premyelocytes doubled the averages of the infants and young. The metamyelocytes ranged higher than in infant and young monkeys. Adult polymorphonuclear neutrophils amounted to a little more than in the younger animals, while polymorphonuclear eosinophils and basophils averaged a little less than in the young and infant monkeys.

The lymphocytes appeared almost equal to the count in infants, but fewer than in young animals. The monocytes were found to

be present in larger numbers in the adults than in the younger animals. The percentage of plasma cells was a little higher than in young, and very much greater than in the infant animals. In none of the samples were megakaryocytes encountered, except in two adults.

The erythrocytic component of the bone marrow in infant and young monkeys is found to be higher than in the adult animals. The granulocytic component is higher in the adult than in either young or infant, and there is a gradual decrease with age, in contrary to the erythrocytic component. The lymphocytic series were in total higher in the infant and young than in the adult animal. It is interesting to notice that even in the adult monkeys, the lymphocyte count was high.* Ratios of erythrocytic to granulocytic series were as follows: Infants, 1 to 2.8; young, 1 to 3; and adults, 1 to 4.

Morphologically, the cells resemble those of the human bone marrow. The number of lobes of the nuclei of the polymorphonuclears were numerous in some cases. The lymphocytes appeared to be larger in size than in human marrow and a great number showed many coarse granules in the cytoplasm. With the exception of 2 cases, megakaryocytes were totally absent. Many "loose" nuclei resembling reticulo-endothelial cells were encountered, but in a very few cases was a definite cytoplasmic component seen in these cells.

Comment. In this study it should be noted that these monkeys live in the most natural of habitats and were caged only for a day or two before our experiments were practiced. Thus, the animals led their natural life as nearly as possible.

The bone marrow picture of the infant monkey was characterized by a higher count in megaloblasts, early erythroblasts, late erythroblasts and normoblasts than in the young or adult animals; but the number of cells of the granulocytic series was lower in the infant than in the young or adult. The lymphocytes were more numerous in the infants' marrow than in the adults', but equal to the young animals. The same thing may be said about the bone marrow of the young monkey, which appeared to present the same picture as the infant in relation to the adult.

The ratio of the erythrocytic series to the granulocytic series gradually decreased with age. Megakaryocytes were found only in two adult samples. Tables of ranges and averages in per cent for each of the cellular components of the bone marrow are presented in this paper.

* The difficulty of distinguishing between lymphocytes and the more immature types of nucleated erythrocytes in the bone marrow suggests another possible explanation for this observation.—EDITOR.

Summary. 1. Forty Macacus rhesus monkeys were submitted to bone marrow aspirations in order to study the marrow picture of this animal.

2. All the monkeys, of which 4 were infants, 8 young and 28 adults, live in the most natural of habitats, approaching the most perfect way of life for the animal.

3. The average erythrocytic series in the infant is higher than in either young or adult marrow.

4. The average granulocytic series is higher in the adult than in either infant or young; the young animals' marrow being richer in those cells than the infants'.

5. The young monkey has more erythrocytic cells in its marrow than the adult.

6. The lymphocytes are more numerous in the infant and the young than in the adult monkey's marrow.

7. The ratio for erythrocytic and granulocytic components were found to be as follows: For the infant 1 to 2.8, for the young 1 to 3, and for the adult 1 to 4.

8. Morphologically the cells of the bone marrow resemble those of the human, except for the multiple lobulations of the nuclei of the polymorphonuclear leukocytes and for the larger size of the lymphocytes of the animal.

9. Megakaryocytes were seen in very low percentages (0.2) in only 2 adult animals; none were seen in either young or infants.

10. If it were not for the high number of lymphocytes the bone marrow of the monkey would approach the picture of the human at different stages of life.

This work could not have been possible without the coöperation of Mr. Michael Tomilin in charge of the Cayo Santiago Primate Colony, and the valuable and disinterested technical assistance of Misses Rosario Vázquez and Clemencia Benitez, to whom we are greatly indebted.

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STUDIES ON THE HEMORRHAGIC AGENT 3,3′-METHYLENEBIS (4-HYDROXYCOUMARIN)

PART III. A REPORT ON FURTHER CLINICAL OBSERVATIONS*

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IN previous publications[2,11,12] we reported on 3,3′-methylenebis (4-hydroxycoumarin),† a drug that has become available synthetically through the work of Link and his associates.[4,5,6,8,13,17] It is the purpose of this report to briefly cite other experiences which indicate additional possible usefulness of this drug.

Previous papers have demonstrated that Dicumarol is capable of prolonging the prothrombin time and coagulation time in dogs and human beings *in vivo* when administered orally, or intravenously in the form of disodium salt. The effects are noticeable only after 24 hours or more, regardless of the size of the dose. The drug is reasonably safe, but because individual responses vary considerably, the dosage must be controlled by daily or almost daily determinations of the prothrombin time and coagulation time. In most instances these roughly parallel each other. The drug appears to have no effect on the functions of the liver or kidneys as tested by the prothrombin time, the hippuric acid test of Quick,[16] the cephalin-cholesterol flocculation test of Hanger,[7] determination of the serum proteins and non-protein nitrogen, urinalysis, and the phenolsulphonphthalein test before and after the periods of observation. In 29 dogs, several of which were killed with the drug, no significant hepatic or renal changes, either gross or microscopic, were demonstrated. On the other hand, rather widespread dilatation of capillaries, arterioles and venules was frequently noted. In human beings no toxic manifestations other than hemorrhage were demonstrated; this was ordinarily microscopic, but in 1 instance, gross hemorrhage from the operative site. Vitamin K, even when administered in large doses, did not reduce the prolonged prothrombin time, but transfusion of fresh blood was antidotal.

It was concluded that the drug might well have a place in clinical

* This investigation has been aided in part by a grant from the Wisconsin Alumni Research Foundation.

† Dicumarol is the collective trademark for 3,3′-methylenebis (4-hydroxycoumarin) of the Wisconsin Alumni Research Foundation which controls the use thereof.

medicine in the prevention of thromboses and as a substitute for heparin in other conditions. It should, however, be used with caution; patients with hemorrhagic tendencies or gross hepatic disease should not receive the Dicumarol. The proper dosage, in our experience, varies with the patient, but 80% of our cases responded satisfactorily to an original dose of 5 mg./kg. followed by the daily administration of 1.5 mg./kg. On certain days no dose was given if the prothrombin time or coagulation time was too prolonged. The aim was to maintain the prothrombin time at about 15 seconds, not beyond 19 seconds (25%), and the coagulation time between 15 and 20 minutes. Since the early reports appeared, others[1,10,18,19,20] have made clinical studies, and in the main these corroborate the experiences of Butt, Allen and Bollman[3] and our own.

Methods. The methods employed have been described in previous papers. For each patient a complete blood study and routine urinalysis was made. No patient was given the drug before the bleeding time, coagulation time, prothrombin time, and capillary fragility were measured. The normal prothrombin time, measured by the method of Quick as modified by Pohle and Stewart[14] was 9.5 to 10.5 seconds. Always the technique and potency of the thromboplastin were checked by testing one or more untreated individuals each day. The coagulation time was measured by the 2-tube method of Lee and White,[9] as modified by Pohle and Taylor.[15] The normal time by this method is, in our hands, between 6 and 14 minutes.

Use With Heparin. It is obvious that the latent period of 24 hours or more is disadvantageous to the patient with a recent thrombosis. Hence the possible value of using an anticoagulant during the latent period was considered. It has already been stated that there was no theoretical objection to the use of heparin and Dicumarol combined. The case described below, 1 of 3 treated with both heparin and Dicumarol seems to demonstrate the value of the simultaneous use of the two substances.

Case 1.—A 62-year-old white male, a railroad engineer, was admitted (service of Dr. M. G. Masten) on 12-9-41. On the previous day he had developed numbness and weakness of the left arm and leg. These symptoms increased. For a month he had had some pain in the occipital region. Physical examination showed alertness, weakness of the left hand and left side of the face, some dysarthria, deviation of the tongue to the left, tortuosity of the retinal arteries, and a blood pressure of 170/104. It was believed that the patient had a cerebral thrombosis; later it was concluded that the occlusion was of one of the ascending branches of the middle cerebral artery. On the day of admission the coagulation time and prothrombin time were both normal, and heparin was administered subcutaneously and Dicumarol orally. The total dosage of heparin during the 3-day period of its administration was 395 mg. The response to these drugs is shown in the chart. The recovery was rapid and the patient left the hospital on 1-10-42. Follow-up studies in the outpatient department have shown a satisfactory condition, and the patient has been back at work.

The chart shows that the prothrombin time increased on the third day of Dicumarol administration. With this evidence of the effectiveness of the drug, the heparin was stopped, and Dicumarol alone was administered. It appears that this procedure is logical and worthy of consideration in cases

where immediate prolongation of coagulation is desirable, although there is no question that intravenous is preferable to subcutaneous administration of heparin.

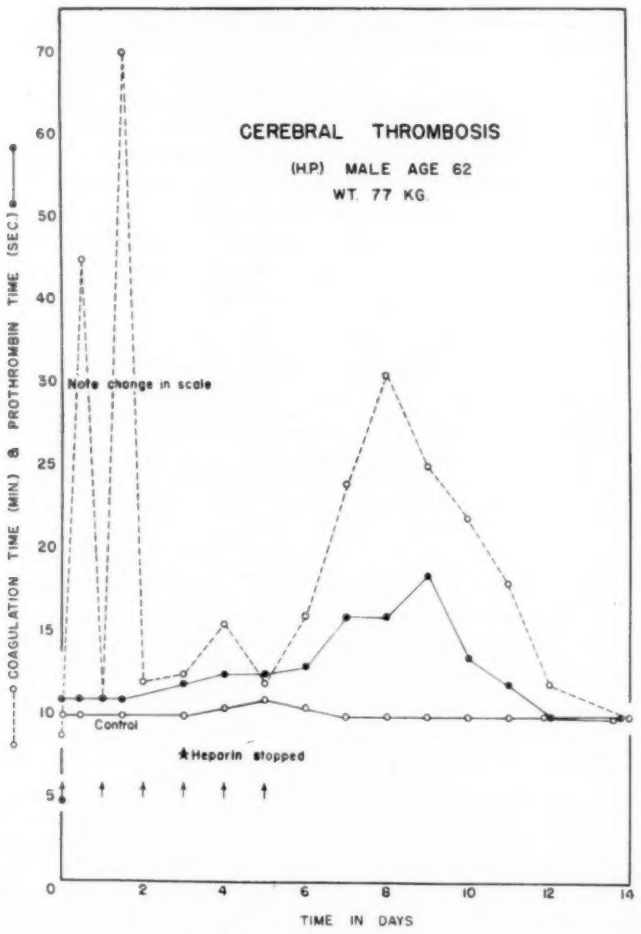

CHART 1.—The effect of combined administration of heparin (total of 395 mg.) and Dicumarol (↕ = initial dose of 5 mg./kg.; ↑ = daily dose of 1.5 mg./kg.) upon the coagulation time in a case with cerebral thrombosis.

Subacute Bacterial Endocarditis. The results of the combined use of heparin and sulfonamides in the treatment of subacute bacterial endocarditis have not, in many instances, been happy. Fatal cerebral hemorrhages have been reported. On theoretical grounds the employment of Dicumarol in combination with a sulfonamide is less logical than the use of heparin. Nevertheless, because of several inquiries we treated 2 cases, 1 a boy of 14 with pneumococcus

Type VI infection engrafted upon a rheumatic endocarditis, and a second case, shown in Chart 2. The first patient was treated for only 15 days, the second for a total of 81 days (50 days of which are

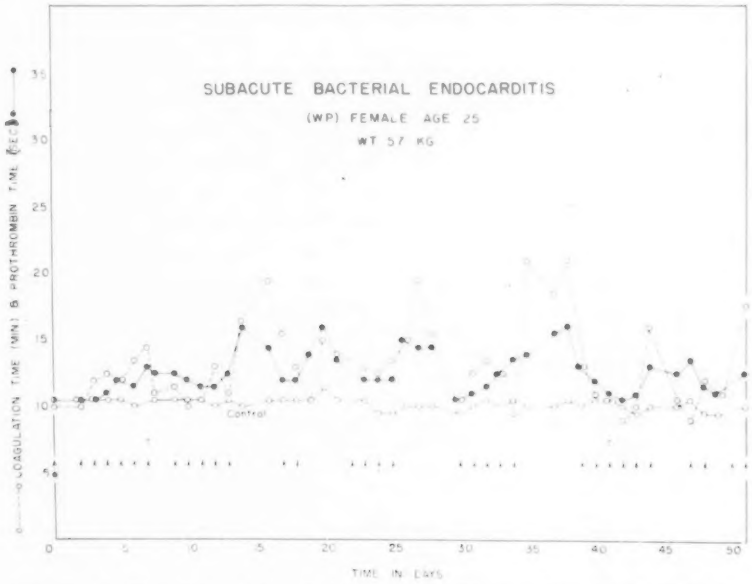

CHART 2.—The effect of the administration of Dicumarol combined with sulfadiazine for a protracted period to a patient with subacute bacterial endocarditis (streptococcus viridans; ↓ = 5 mg./kg. ↑ = 1.5 mg./kg.; T = transfusion of blood).

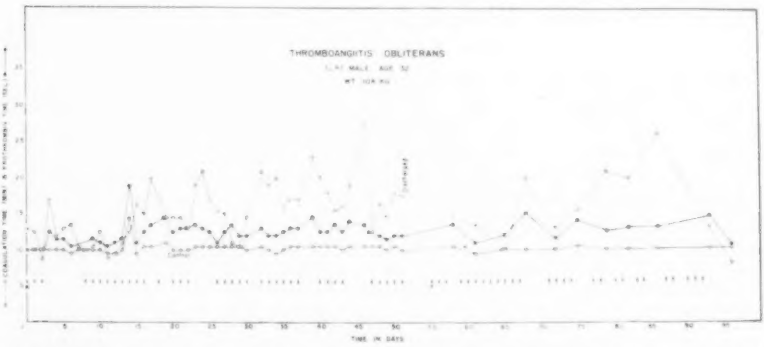

CHART 3.—The effect of prolonged administration of Dicumarol to a patient with Buerger's disease. Total dosage approximately 10 gm. (↓ = 5 mg./kg.; ↑ = 1.5 mg./kg.; ↕ = 3 mg./kg.).

depicted in the chart). In neither instance was any untoward effect observed, nor was any benefit demonstrated, although the coagulability of the blood was decreased in both. In the patient treated

for 81 days the liver function was unaffected by the protracted administration of Dicumarol. This patient died of her disease on June 12, 1942, more than 5 weeks after the Dicumarol was stopped. Gross and microscopic postmortem studies of the liver and kidneys showed only the changes attributable to subacute bacterial endocarditis. Despite these 2 cases, however, in which no accident occurred, the use of Dicumarol is deemed unwise, as others[1] have observed cerebral hemorrhage and death resulting from this type of therapy. Allen[1] has advised that the drug be avoided or used only with great caution in subacute bacterial endocarditis.

Prolonged Use of Dicumarol. In occasional cases it may be desirable to administer Dicumarol for periods of many weeks. In the light of the case reported above and that depicted in Chart 3, this is regarded as permissible.

Case 2. A white male of 32, with mild thromboangiitis obliterans, obtained relief of pain during treatment, but whether or not the Dicumarol was responsible was not definitely established. Thus far he is the only patient that has been treated as an out-patient, and then only after a considerable period of hospital observation, and the only patient that was not observed almost daily with determinations of the prothrombin time and coagulation time. Liver function tests at the conclusion of the period of treatment were normal, as they had been prior to the institution of therapy. During the 92-day period of treatment the drug was administered 62 times for a total of approximately 10 gm.

Case With Hemorrhage. Although the appearance of blood in the urine as demonstrated by a positive benzidine test is not unusual, and may occur in about 15% to 20% of cases treated with Dicumarol, gross bleeding occurred in only 2 of the first 100 cases treated. The first experience of bleeding from an operative site has been reported. A second case is here reported, because this patient was more sensitive to Dicumarol than any other we have encountered.

Case 3. A white male of 65 was admitted to the Urological Service on 3-5-42, with the complaint of bloody urine. Cystoscopic inspection of the bladder demonstrated a carcinoma, and on 3-23-42 a total cystectomy and prostatic enucleation were performed. Because of the wide exposure of the pelvic veins, administration of Dicumarol was advised. On 3-24-42 the patient received a total of 325 mg. (5 mg./kg.) and on 3-25-42, 98 mg. (1.5 mg./kg.). The drug was then stopped because of the unusually prompt and marked effect. Gross hemorrhage was observed 2 days later, as depicted in Chart 4. Undetected hemorrhage may have been present elsewhere, for the hemoglobin fell from a preoperative level of 11.8 gm. to 6.4 gm. on 3-30-42. A persistent anemia was noted thereafter and only gradually did the hemoglobin increase to 10.1 gm. by 5-2-42. His condition was precarious. It was deemed necessary to give 5 transfusions, each of 500 cc., between 3-28-42 and 4-1-42, 2 of them on 3-28-42. The patient finally improved sufficiently to be discharged on 6-6-42.

This patient had had cyclopropane-ether anesthesia. The question immediately comes to mind, Did the anesthesia impair the liver so that the patient was thus more markedly affected by the Di-

cumarol? The assumption is logical if we accept the theory that the action of Dicumarol depends upon physiologic inhibition of the liver. Also, a Hanger's test in this patient was 4+ on 3-28-42, but negative on 4-7-42. This matter has been recently investigated by testing the relative sensitivity of anesthetized and unanesthetized dogs.

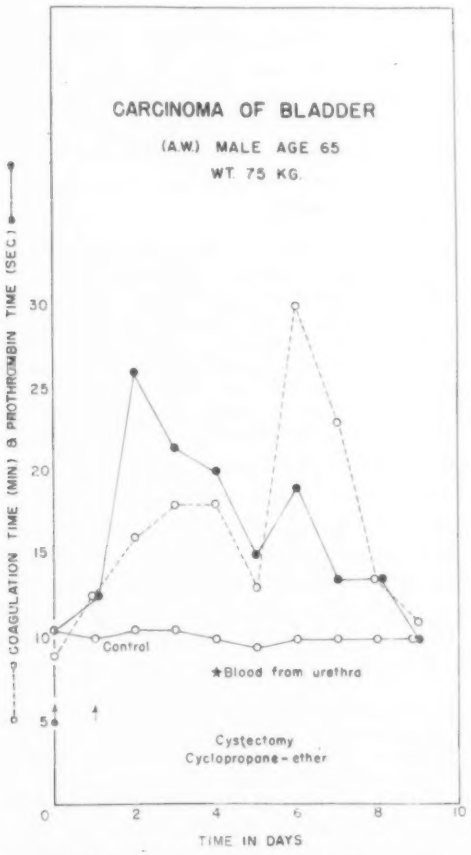

CHART 4.—The marked effect of administration of Dicumarol to a postoperative case. Cyclopropane-ether anesthesia was administered for about equal periods for a total of 80 minutes (● = 5 mg./kg.; ↑ = 1.5 mg./kg.).

Effect of Dicumarol on Anesthetized Dogs. Three dogs were anesthetized with cyclopropane for 30 minutes and 3 additional dogs were anesthetized for 45 minutes with cyclopropane and ether for equal periods. The last 3 dogs were given $\frac{1}{4}$ gr. (0.015 gm.) to $\frac{1}{3}$ gr. (0.020 gm.) of morphine subcutaneously 2 hours prior to the induction of anesthesia; the first 3 received none. On the day after the anesthesia, each dog was given 5 mg./kg. of Dicumarol orally, and the 3 unanesthetized control dogs were given a similar dosage.

The total doses ranged from 47.5 to 116 mg. Thereafter for 10 days the prothrombin time and coagulation time were measured daily. The response in the unanesthetized dogs was as marked as in the experimental animals; hence no increased sensitivity of normal animals was discernible. This lessens the likelihood that anesthesia was responsible for the condition in the above-described patient, but it does not, of course, exclude the possibility, nor does it obviate the necessity of attention to this detail in other postoperative cases.

Discussion. It is hoped that the report of these additional experiences with the use of Dicumarol will be of aid to others who are employing or plan to employ this interesting drug in clinical investigations. As our experience has grown, we have used it with less and less fear of untoward effects. It is still our feeling after treating 105 patients that an approximate oral dose of 5 mg./kg. followed by the daily administration of 1.5 mg./kg. is reasonably satisfactory and gives the most stable level of prolonged prothrombin time and coagulation time, although repeated doses at intervals of about 3 or 4 days are also permissible. When the disodium salt of 3,3′-methylenebis (4-hydroxycoumarin) is given intravenously, it is our custom to give 4 mg./kg. at intervals of 3 to 5 days. No matter how the drug is administered, repeated (preferably daily) determinations of the prothrombin time and coagulation time is imperative. The induction of a prolongation of the prothrombin time to below 25% of normal is almost certainly unwise, and probably maintenance of the coagulation time at between 15 and 20 minutes is satisfactory.

Dicumarol is still in the stage of active investigation, and its indiscriminate use is hazardous. It has, however, been demonstrated that it may be given for periods as long as 90 days without producing subjective symptoms or detectable undesirable objective findings. The mechanism by which the drug acts has not yet been established, and one should be on guard for the possible case with an idiosyncrasy whence, on theoretical grounds at least, one might anticipate the production of serious hepatic disease. To date, we have not experienced any untoward effect other than hemorrhage from operative sites.

The question of the actual value of Dicumarol in preventing thrombosis in patients, a question of major importance, is still unsettled, and only extensive investigations with large, well-controlled series will furnish the answer. The theoretical basis for its use is sound, for when properly used it is capable of producing hypocoagulability of blood.

Conclusions. 1. Continued studies with Dicumarol-3,3′-methylenebis (4-hydroxycoumarin) have further established its efficacy in prolonging the prothrombin time and coagulation time in human beings.

2. Administration of Dicumarol may be safely combined with heparin administration when prompt prolongation in the coagula-

tion time is desired. When the prothrombin time is prolonged, evidence of Dicumarol effectiveness, the heparin may be omitted.

3. The use of sulfonamides and Dicumarol in combination does not appear to be of value in the treatment of subacute bacterial endocarditis. This therapy is not advised.

4. As much as 10 gm. of Dicumarol has been administered over a 92-day period to a patient with thromboangiitis obliterans with symptomatic improvement, and without detectable changes in liver function.

5. A second case with gross hemorrhage from an operative site after a small total intake of Dicumarol is reported. It was suggested that general anesthesia such as cyclopropane ether, which was used in this case, might possibly make the patient more sensitive to Dicumarol. Possibly smaller than average doses should be employed. However, experimental studies in dogs do not substantiate this tenet.

6. The initial dose of 5 mg./kg. followed by daily doses of 1.5 mg./kg. still appears to us to be reasonably satisfactory in most patients.

7. Reiteration of the importance of caution in employment of this potent drug is deemed proper. Dicumarol is still under investigation, and should not be used unless thoroughly reliable facilities for daily accurate determinations of the prothrombin time and coagulation time are readily available.

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BOOK REVIEWS AND NOTICES

OUTLINE OF PSYCHIATRIC CASE-STUDY: A Practical Handbook. By PAUL WILLIAM PREU, M.D., Assistant Professor of Psychiatry and Mental Hygiene in the Yale University School of Medicine, Physician-in-Charge of the Psychiatric Clinic of the New Haven Hospital, Associated Psychiatrist to the New Haven Hospital. Pp. 279. Second Edition. New York: Paul B. Hoeber, Inc., 1943. Price, $2.75.

STIMULATED by the methods of Adolph Meyers and others, the author brought together the material for his first edition 3 years ago. The Outline is intended as an aid in bringing out the facts upon which the diagnosis and treatment shall rest.

The first part of the book is an Outline of Psychiatric History-Taking and Behavioral Examination for Use With the Adult. It includes the complaint, present social situation, background of the problem, family history, social-psychiatric history, personality, medical history and previous psychiatric illness or problem. Included in the Behavioral Examination are general appearance, behavior attitude content, topics of preoccupation, emotional state, stream of speech, consciousness, memory, intellectual capacity and insight. A special part considers procedure when the patient is stuporous or comatose.

The second section discusses the Outline of Psychiatric History-Taking and Behavioral Examination for Use With the Child, where much of the information is obtained from the mother or other interested person. Such data is often more complete than that given by an adult whose early life cannot be recalled. The subject matter of this handbook is well suited to the purpose designated. N. Y.

VIRUS DISEASES. By Members of the Rockefeller Institute for Medical Research; THOMAS M. RIVERS, M.D., WENDELL M. STANLEY, PH.D., LOUIS O. KUNKEL, PH.D., RICHARD E. SHOPE, M.D., FRANK L. HORSFALL, JR., M.D., and PEYTON ROUS, M.D. Pp. 170; several plates. Ithaca, N. Y.: Cornell Univ. Press, 1943. Price, $2.00.

THIS book consists of the Messenger lectures, given at Cornell University by 6 specialists in the field of viruses. Thomas M. Rivers discusses the nature of viruses. He takes as an example vaccinia and tells what has been learned of its physical, chemical and immunologic properties. Under the electron microscope, the elementary bodies appear to have some sort of internal structure and a limiting membrane.

W. M. Stanley speaks of passing viruses through suitable hosts, thus causing the viruses to mutate. It is such mutants that are used in immunizing against smallpox, rabies and yellow fever.

Swine influenza is discussed by R. E. Shope. Between epizoötes, the virus lurks in an intermediary host, the lung worm, which itself has an intermediary host, the earth worm.

Human influenza is divided by F. L. Horsfall into paradémic, epidemic and endemic types. For each type he discusses the etiologic rôle of viruses and bacteria.

Which tumors are caused by viruses and how these agents act to cause tumors, is the subject of the lecture by Peyton Rous.

These lectures are quite readable, are not highly technical, and bring the subject up to date. M. M.

PSYCHOSOMATIC MEDICINE: The Clinical Application of Psychopathology to General Medical Problems. By EDWARD WEISS, M.D., Professor of Clinical Medicine, Temple University Medical School, and O. SPURGEON ENGLISH, M.D., Professor of Psychiatry, Temple University Medical School. Pp. 687. Philadelphia: W. B. Saunders Company, 1943. Price, $8.00.

ONE of the latest developments in our profession is the appearance of psychosomatic medicine, about which a special periodical is already published. This subject, "at the present time embraces the neuroses plus an extension of our knowledge of the neuroses to the psychopathology of other conditions previously thought to be in the realm of purely physical medicine." It is claimed one-third of all patients come under this classification, and that another third show symptoms dependent in part upon emotional factors. "The busy practitioner can read the first two chapters and the last four and get a general idea of the subject." As here described, the psychologic relation of the mental processes, shows a decided Freudian coloring; in the diagnosis of personality trends, high tribute is paid to the somewhat neglected Rorschach ink-blot tests.

Throughout the 23 chapters there are 73 case reports. The part on the gastro-intestinal system in 3 chapters includes functional digestive disturbances, chronic appendicitis, gall bladder disease, mucous colitis, ulcerative colitis, cardiospasm, anorexia nervosa, and peptic ulcer. Genito-urinary and sexual disorders consider instinctual forces, genital functioning, education in sexuality, emotions and menstruation, dysmenorrhea, amenorrhea, frigidity and impotence. Three chapters on the endocrine system and metabolism, include emotional life and ovarian function, menopausal syndrome, male climateric, puberty, relation of disorders of the thyroid gland, Addison's disease and the adrenal syndrome, diabetes mellitus, hyperinsulinism, and obesity.

A chapter on military medicine is well balanced. In a few chapters some subjects are considered too briefly, such as alcohol and drug addicts, which are accorded scarcely a dozen lines. There is a want of formal neurologic examinations. Being teachers, these authors advocate first-year instruction in psychobiology to parallel that of physiology and anatomy. In the second year the psychologic processes of adolescence should be correlated with those of physiology and endocrinology. The third year should give combined lecture and case presentation. In the final year, that knowledge already acquired should be applied in the ward, class and clinic. The book gives many references and a comprehensive index covers more than 26 pages.

N. Y.

UNDERSTAND YOUR ULCER. By BURRILL B. CROHN, M.D., Associate in Medicine, Gastro-Enterology, Mt. Sinai Hospital, New York; Associate in Medicine, Columbia University. Pp. 199; 19 illustrations. New York: Sheridan House, 1943. Price, $2.50.

IN this book Dr. Crohn has done for the peptic ulcer patient what Dr. Joslin has done for the diabetic. It is the sort of book every gastro-enterologist has wanted to write. It covers the things the ulcer subject should know and what any good personal physician would tell him if he had the time. Many will not agree with every statement, but for the lay reader's sake the author has done well to avoid controversial issues and has shown excellent judgment, without misleading his reader, in omitting observations that might produce undue alarm. Part II, on diets, by SYLVIA BAYARD, is well done and will be found extremely helpful not only to the ulcer patient but also to the practising physician. Dr. Crohn is to be congratulated on a work that is certain to be popular at this time and to require many revisions.

T. M.

ADVANCES IN INTERNAL MEDICINE, VOL. I, 1942. New York Number. Editor, J. MURRAY STEELE, M.D., Welfare Hospital, New York University Division, Welfare Island, N. Y. Pp. 292; many figures and tables. New York: Interscience Publishers, Inc., 1942. Price, $4.50.

THIS is the initial volume of a new series of medical publications, prepared under the supervision of Dr. J. Murray Steele, as editor, and a group of highly qualified associates, consisting of Drs. William Dock, Tinsley R. Harrison, Chester S. Keefer, Robert F. Loeb, Warfield T. Longcope, George R. Minot, and I. Snapper. Each of the 10 presentations covers about 30 pages and consists of a review of a field of clinical medicine to which the author himself has made significant contributions and which is regarded as representing an advance in knowledge. The book affords the author an opportunity to present at greater length and more informally than can be done in an ordinary journal his personal viewpoint about his special subject. A list of the authors and the titles of their presentations is sufficient to indicate the character and importance of this first volume. The use of the Miller-Abbott tube in diagnosis and treatment is covered by W. Osler Abbott; use of insulin and protamine insulin in diabetes, by Paul Levietes; sympathetic nervous control of the peripheral vascular system, by Robert W. Wilkins; the antibacterial action of the sulfanilamide drugs, by Colin M. MacLeod; the choice of the sulfonamides in treatment, by Chester S. Keefer; infections of the urinary tract, by Lowell A. Rantz; epidemic influenza, by Thomas Francis; hypertension, by Irvine H. Page; nephrosis, by Lee E. Farr; and riboflavin deficiency, by Harold Jeghers.

Whether or not the medical public will support and profit by such a publication remains to be seen, but at least this volume, because of the choice of authors and subjects and because of the care with which the papers have been prepared, including in each instance an extensive bibliography, deserves the attention of all those who are making an effort to keep themselves informed about the advances in the broader field of clinical medicine. T. M.

MICROBIOLOGY AND MAN. By JORGEN BIRKELAND, PH.D., Assistant Professor of Bacteriology, Ohio State University, Columbus, Ohio. Pp. 478; 35 figures, 9 charts. Baltimore: Williams & Wilkins Company, 1942. Price, $4.00.

THIS book is designed as an elementary text for the student who plans to take but one or two courses in microbiology. It is intended to serve as a basis for an understanding of the part played by microörganisms in everyday life. It is a guide for learning as well as a source book of facts. Part I (130 pages) is devoted to the fundamentals of microbiology. Part II (48 pages) is a very brief discussion of infection and resistance. Part III (184 pages) is devoted to a discussion of specific infectious diseases. Diseases caused by bacteria, rickettsiæ, and filterable viruses are included in the discussion, but not those diseases caused by animal parasites or fungi. An unfortunate error occurs on page 235 where it is stated that diphtheria toxoid is prepared by treating diphtheria toxin with formalin or by precipitating with alum. The omission of the genus *Clostridium* is not so excusable. No mention is made of tetanus or gas gangrene. *Cl. botulinum* is described under food poisoning, *Cl. welchii* is briefly mentioned only as an anaërobic spore former which may be used as an indicator of pollution, and *Cl. butyricum* is mentioned in relation to nitrogen fixation. Even a discussion of the methods for growing microörganisms anaërobically is missing from the book. Part IV (76 pages) is a discussion of the microbiology of food, milk, water, sewage, and soils. The appendix consists of a summary of the classification of the Class Schizomycetes, a glossary of terms, and a list of selected references. H. M.

OPHTHALMOLOGY AND OTOLARYNGOLOGY. Military Surgical Manuals, II. Prepared and edited by the Subcommittee on Ophthalmology and Otolaryngology of the Committee on Surgery of the Division of Medical Sciences of the National Research Council. Pp. 331; 51 figures. Philadelphia: W. B. Saunders Company, 1942. Price, $4.00.

THIS is one of a series of 6 volumes known as the "Official Military Surgical Manuals." These manuals have been prepared and edited by the various subcommittees under the auspices of the Committee on Surgery of the Division of Medical Sciences of the National Research Council, with the coöperation of the Surgeons-General of the U. S. Army and Navy.

The general purpose of these volumes is to acquaint the physicians in our armed forces with officially approved methods, techniques, and treatments. "Ophthalmology and Otolaryngology" succeeds in its effort to supply clear, practical, and authoritative information concerning diagnosis and treatment of specific conditions of the eye, ear, nose, and throat. Twenty-three outstanding authorities handle a tremendous amount of material facilely, briefly, and explicitly. The chapters are well defined, the information is clearly organized and edited, and the book is nicely illustrated.

Although the specialist will probably find this manual too condensed for his purposes, the Army and Navy physician should have little difficulty in using it profitably as a practical guide and reference. I. L.

WAR AND THE DOCTOR. ESSAYS ON THE IMMEDIATE TREATMENT OF WAR WOUNDS. Edited by J. M. MACKINTOSH, M.D., Chief Medical Officer of the Department of Health for Scotland. Pp. 135. Second Edition. Baltimore: William Wood & Co., 1942. Price, $2.00.

As stated by the editor, this book is a monograph made up of a series of lectures delivered at the request of the Edinburgh branch of the British Medical Association. These lectures were given by men whose battle experience dated from the war of 1914–1918. It is lacking in the experience that has been derived from the present conflict. Shock and hemorrhage is discussed without any reference to blood plasma. The surgical sections do not include any of our present knowledge of the use of sulfanilamide compounds. This gives a sense of unreality to what is otherwise a fairly adequate discussion of the surgical problems arising from war. Its greatest lack is that it does not cover the medical problems as they actually have developed. J. H.

DISEASES OF THE LIVER, GALL BLADDER AND BILE DUCTS. By S. S. LICHTMAN, M.D., F.A.C.P., Adjunct Physician, Mount Sinai Hospital; Assistant in Post-Graduate Medical Instruction, University Extension, Columbia University, New York. Pp. 906; 122 illustrations. Philadelphia: Lea & Febiger, 1942. Price, $11.00.

THIS textbook presents a review of much of the literature on the anatomy, physiology, and diseases of the liver and the biliary system. The arrangement of its contents is unusual in that the author begins with a discussion of the microanatomy of the hepatic lobule, then in the chapters on the functions of the liver, its exogenous poisons, its morbid anatomy, the symptomatology and etiology of its diseases and its functional tests, he discusses in detail many purely clinical problems which have to be reconsidered when finally (page 355) he takes up the specific hepatic diseases. In spite of a formal and helpful classification of the functional tests (page 252), he later confuses the matter by taking up various tests applicable to the blood under the heading of those applicable to the urine (bromsulphthalein for instance). He repeatedly uses the word "data" in the singular.

The discussion of clinical entities, including affections of the gall bladder and biliary ducts, is very complete, but makes unnecessary reference to much of the older literature; in the end the Reviewer is often left in doubt regarding the author's own viewpoint. Apparently he regards hepatitis only as a disease of the liver of unknown etiology, referring separately to the affections resulting from known agents, such as arsenic, phosphorus, chloroform, toxic jaundice. This is at variance with the usual custom. Many of the illustrations are excellent. The book will be found useful mainly as a book of reference. T. M.

THE HOSPITAL CARE OF THE SURGICAL PATIENT. By GEORGE CRILE, JR., M.D., Surgeon, Cleveland Clinic; and FRANKLIN L. SHIVELY, JR., M.D., Assistant Surgeon, Cleveland Clinic. Pp. 184; 21 figures. Springfield, Ill.: Charles C Thomas, 1943. Price, $2.50.

THIS small volume is an extremely valuable asset to anyone caring for surgical patients. It cannot be recommended too highly for the surgical interne and resident; it foresees his every problem and includes a practical discussion of the procedures and complications arising every day in the hospital management of patients subjected to surgery.

The first section deals with the physiologic principles of water and chemical balance related to the care of the patient before and after operation. The second section is an admirable discussion of the management of postoperative complications. An acceptable, standardized technique for routine hospital procedures is presented in the third section. In each instance, care is taken to point out limitations and dangers as well as the actual indications. All who wish to keep in touch with the newer procedures employed to make an operation safe will find this book invaluable.

L. S.

MENTAL HEALTH IN COLLEGE. By CLEMENTS C. FRY, M.D., Lecturer in Psychiatry and Mental Hygiene and Psychiatrist to the Department of University Health, Yale University; with the collaboration of EDNA G. ROSTOW, Research Assistant in Psychiatry and Mental Hygiene, Division of College Psychiatry and Mental Hygiene, Yale University. Pp. 384. New York: Commonwealth Fund, 1942. Price, $2.00.

THIS is a descriptive analysis of adjustment problems in Yale students treated during a 10-year period by the Division of College Psychiatry and Mental Hygiene.

The materials are drawn from case studies and are presented in case study form. Cases used represent varying degrees of maladjustment arising from a wide variety of causes and conditions. Procedures in treatment are outlined and results reported in those cases in which follow-up was made. Cases with certain common characteristics are grouped together and discussed. The authors emphasize, however, that the causes of a given adjustment problem are almost invariably complex and interactive, and that each problem must be studied individually, rather than treated as a "type."

Certain causal elements appearing frequently in the student cases grow out of (1) family relationships, (2) worries related to sex, and (3) parental or social "pressure for success."

The book does not contain explicit suggestions concerning improvement of the college environment to the end of reducing the incidence of mental ill-health. There are, however, many implications which should be noted by all readers who have responsibility for mental health conservation in college students. T. M.

FAMILIAL NON-REAGINIC FOOD ALLERGY. By ARTHUR F. COCA, M.D., Medical Director, Lederle Laboratories. Pp. 160; 20 tables, 12 charts. Springfield, Ill.: Charles C Thomas, 1943. Price, $3.00.

THE author presents very concisely a new method of approach to the diagnosis and treatment of a relatively large group of allergic diseases (migraine, urticaria, gastro-intestinal allergy, neuralgias, and a number of more or less serious conditions hitherto usually not recognized as allergic such as canker sores, constipation, nervousness, physical tiredness, chronic rhinitis, epileptiform seizures, even some cases of hypertension, and others). No implication is made that the above conditions are always allergic in origin, but by rather definite signs and symptoms he is able to select those that are. A surprisingly high incidence in these conditions has by the author's criteria of diagnosis been found to be of allergic origin, and accordingly the therapeutic test usually confirmed it.

The category of allergic disease designated as familial non-reaginic food-allergy is identified by the following points: Its characteristic symptomatology, the failure of the usual cutaneous tests, a separate hereditary influence, and the regular effect of an acceleration in the pulse rate. The author reports that without exception in the first 44 cases who completed the course of dietary treatment, when the pulse rate had reached the level and range that was recognized as normal for the individual, the chief symptoms completely disappeared.

Within this brief monograph are reported detailed methods of diagnosis and treatment with results in this type of allergy, and a discussion concerning the nature of this disease process. To the Reviewer the contents of this book seem to offer great hope and encouragement for the better identification and management of a significant number of common yet frequently distressing conditions seen by the clinician. A more extensive trial of the procedure described is needed, and the reported results would seem only to hasten this. M. T.

CARCINOMA OF THE STOMACH. By WALTMAN WALTERS, B.S., M.D., M.S. in Surgery, D.Sc., F.A.C.S., Surgeon, Mayo Clinic; Professor of Surgery, University of Minnesota (Mayo Foundation); Commander, Medical Corps, United States Naval Reserve; Diplomate of the American Board of Surgery; Member, National Advisory Cancer Council; HOWARD K. GRAY, B.S., M.D., M.S. in Surgery, F.A.C.S., Surgeon, Mayo Clinic; Associate Professor of Surgery, University of Minnesota (Mayo Foundation); Lieutenant Commander, Medical Corps, United States Naval Reserve; Diplomate of the American Board of Surgery; and JAMES T. PRIESTLEY, B.A., M.D., M.S. in Experimental Surgery, PH.D. in Surgery, F.A.C.S., Surgeon, Mayo Clinic; Associate Professor of Surgery, University of Minnesota (Mayo Foundation); Major, Medical Reserve Corps, United States Army; Diplomate of the American Board of Surgery; and Associates in the Mayo Clinic and Mayo Foundation, Rochester, Minn. Pp. 576; 152 figures and 82 tables. Philadelphia and London: W. B. Saunders Company, 1942. Price, $8.50.

THIS monograph is the result of an analysis made on 10,890 cases in which the diagnosis of carcinoma of the stomach was made at the Mayo Clinic between the years 1907 and 1938, inclusive. Concerning its contents, the following can be copied without reservation from the authors' preface: "This book contains a thorough review of malignant lesions of the stomach by the authors and their associates at the Mayo Clinic. These chapters have to do with roentgenographic diagnosis, gastroscopy, the clinical features of malignant lesions of the stomach, the indications for treatment, and the nutritional deficiencies associated with such lesions. There is a

long chapter on preoperative treatment, selection of the anesthetic for a particular patient and a detailed presentation of the various types of surgical technic employed in the extirpation of malignant gastric lesions. The pathologic considerations are presented in two chapters, one by Dr. A. C. Broders and one by Dr. W. C. MacCarty. The postoperative treatment is thoroughly covered. Estimation of prognosis and end-results is accurate because of the very high percentage of follow-up studies that were made and calculation of survival rates covers periods up to twenty-five years subsequent to operation. There is a chapter dealing with roentgenologic treatment of inoperable lesions and a chapter on the operating room set-up from the standpoint of the surgical nurse." This the authors have well accomplished with resort to rather frequent statistical tabulations. The reader is spared academic considerations, and the observations and results are confined to the significantly large number of case records accumulated at that one place. One apparent typographical error is found (p. 108, l. 10) —the second word should read "microcytic" instead of "macrocytic." Although the book is limited to carcinoma (and other malignant neoplasms) of the stomach, the career of the gastric neoplasm is long and pertinent to many of the fields of medicine, so that the usefulness of this book immediately becomes great. M. T.

NEW BOOKS

Diseases of the Breast. By CHARLES F. GESCHICKTER, M.A., M.D., Lieut. Comm., Medical Corps, U. S. Naval Reserve, Director of The Francis P. Garvan Cancer Research Laboratory, Pathologist, St. Agnes Hospital, Baltimore. With a Special Section on Treatment in Collaboration with MURRAY M. COPELAND, A.B., M.D., F.A.C.S., Instructor in Surgery, Johns Hopkins Medical School, Visiting Surgeon and Assistant Oncologist, University Hospital, University of Maryland Medical School. Pp. 829; 593 illustrations. Philadelphia: J. B. Lippincott Company, 1943. Price, $10.00.

Pancreatic Function and Pancreatic Disease Studied by Means of Secretion. By HENRIK O. LAGERLOF, M.D. Translated by HELEN D. DREY. With a Foreword by JOSEPH H. PRATT, M.D. Pp. 289; 50 tables. Printed in Sweden. New York: The Macmillan Company, 1942. Price, $3.50.

Symposium on Office Gynecology. Medical Clinics of North America. Vol. 27, No. 1 (Chicago No.). Pp. 272; 19 figures and tables. Philadelphia: W. B. Saunders Company, 1943. Published bi-monthly. Yearly subscription, paper, $12.00; cloth, $16.00.

Essentials of Gynecology. By WILLARD R. COOKE, M.D., F.A.C.S., Professor and Head of the Department of Obstetrics and Gynecology, University of Texas. Pp. 474; 197 illustrations, including 10 in color. Philadelphia: J. B. Lippincott Company, 1943. Price, $6.50.

Burns, Shock, Wound Healing and Vascular Injuries. Military Surgical Manuals V. Prepared under the Auspices of the Committee on Surgery of the Division of Medical Sciences of the National Research Council. Pp. 272; 20 figures. Philadelphia and London: W. B. Saunders Company, 1943. Price, $2.50.

The Vertebrate Eye. By GORDON LYNN WALLS, Research Associate in Ophthalmology, Wayne University College of Medicine. Pp. 785; 197 figures (3 in color); plates and tables. Bloomfield Hills, Mich.: Cranbrook Institute of Science, 1942. Price, $6.50.

The Sight Saver. By C. J. GERLING. Pp. 202, frontispiece. New York: Harvest House, 1943. Price, $2.00.

Treatment of Fractures. By GUY A. CALDWELL, M.D., F.A.C.S., Professor of Orthopedic Surgery, Tulane University of Louisiana School of Medicine; Senior Visiting Orthopedic Surgeon, Touro Infirmary; Visiting Surgeon, Charity Hospital of Louisiana; Director, Section on Bone and Joint Surgery, Ochsner Clinic, New Orleans. Pp. 303; 92 illustrations. New York: Paul B. Hoeber, Inc., Medical Book Dept. of Harper & Brothers, 1943. Price, $5.00.

This little book presents the treatment of fractures in a clear, concise and practical manner. It is well illustrated with line drawings, most of which are original. The recognition of shock and its most modern treatment thereof is also presented. Those appliances, splints and methods of treatment which have proven their value in many hands, are given preference. An excellent chapter on the treatment of compound fractures is given in minute detail, with particular mention of military conditions, débridement, chemotherapy and transportation. The use of pins and other means of internal fixation are described and recommendations given for their usage.

The author has given his readers a nice, complete, up-to-date and practical view of the treatment of fractures as met by the first aid or the medical attendant under civil and military conditions. E. E.

The Metabolic Cost of Maintaining a Standing Position. By HARRIET GRAHAM MCCORMICK, Associate in Physical Education, Teachers College, Columbia University. Pp. 84; 8 figures. Morningside Heights, N. Y.: King's Crown Press, 1942. Price, $1.25.

The subject matter contains the methods used, calculations, and resulting implications obtained on 50 healthy adult subjects from a study designed to reveal any existing relationship between posture and the variation in metabolic increase in the standing rate over the basal rate, and how body alignment varies with any such existing relationships. Her results reveal that "for the normal, healthy individual of average height and weight, it would seem to make very little difference, as far as energy expenditure alone is concerned, what body alignment he assumes in standing." The detailed study will interest and serve all who are concerned with the basic problem or with the related one of helping individuals to improve their body mechanics and posture. M. T.

The Antigonadotropic Factor. By BERNHARD ZONDEK and FELIX SULMAN, Hebrew University, Jerusalem. Pp. 185; 23 tables. Baltimore: The Williams & Wilkins Company, 1942. Price, $3.00.

This is a systematic alignment of opposing points of view on the nature of "antihormones", or substances responsible for the refractoriness which develops in animals as a result of repeated injections of certain hormones, particularly the gonadotropins.

The literature is extensively reviewed, and unpublished experiments of the authors are included. It deals largely with the immunologic and chemical principles involved in this particular phase of endocrine research. I. Z.

Emotions and Memory. By DAVID RAPAPORT, PH.D., Head of the Department of Psychology, The Menninger Clinic. Pp. 282. Baltimore: The Williams & Wilkins Company, 1942. Price, $3.00.

Renal Lithiasis. By CHARLES C. HIGGINS, M.D., Cleveland Clinic, Cleveland. Pp. 140; 18 figures. Springfield, Ill.: Charles C Thomas, 1943. Price, $3.00.

A Surgeon's Fight to Rebuild Men. An Autobiography. By FRED H. ALBEE, M.D., F.A.C.S., F.I.C.S.; Foreword by LOWELL THOMAS. Pp. 349; 11 illustrations. New York: E. P. Dutton & Co., Inc., 1943. Price, $3.50.

Food Poisoning. By G. M. DACK, PH.D., M.D., Associate Professor of Bacteriology, University of Chicago. Pp. 138; 13 tables. Chicago: The University of Chicago Press, 1943. Price, $2.00.

Bronchiectasis. By JAMES R. LISA, B.S., M.D., Pathologist, City Hospital, Welfare Island, Midtown Hospital, French Hospital, New York; and MILTON B. ROSENBLATT, B.S., M.D., Associate Visiting Physician, City Hospital, Welfare Island, Chief of Medical Clinics and Chief of Chest Clinic, City Hospital Division, Welfare Island Dispensary; Associate Attending Physician in Pulmonary Diseases, Montefiore Hospital. Pp. 190; 35 figures and tables. New York: Oxford University Press, 1943. Price, $4.00.

NEW EDITIONS

Fractures. By PAUL B. MAGNUSON, M.D., F.A.C.S., Associate Professor of Surgery, Northwestern University Medical School, Attending Surgeon, Passavant Memorial Hospital and Wesley Memorial Hospital, Chicago. Pp. 511; 317 illustrations. Fourth Edition. Philadelphia: J. B. Lippincott Company, 1943. Price, $5.50.

This edition maintains the excellent standard of the preceding ones. It further discusses the all-important questions of shock in its various forms and the treatment and handling of fractures under military conditions, with especial emphasis on débridement, chemotherapy and fixation. The use and abuse of plating and the various materials used in their making is considered in all phases. With the exception of some neglect in the index of the volume, the book ranks among those of other authorities on the subject. Furthermore, it is nicely bound, printed and indited. E. E.

The Relation of Certain Anomalies of Vision and Lateral Dominance to Reading Disability. By PHILIP W. JOHNSTON. Monographs of the Society for Research in Child Development. Vol. VII, Serial No. 32, No. 2. Pp. 153; many tables and figures. Published by Society for Research in Child Development, National Research Council, Washington, D. C., 1942. Price, $1.50.

It takes 147 pages of statistics to prove that "any observed association between anomalies of dominance and reading disability in the case of children born between the dates of October 1, 1926, and May 31, 1937, and attending the Public Schools of Reading, Mass., can be explained on the basis of fluctuations due to the operation of chance factors." Doubtless such information has to be obtained, but it is somewhat like analyzing the rat's tail for arsenic for the reason that it has never been done before. F. A.

Medical Jurisprudence and Toxicology. By JOHN GLAISTER, M.D., D.Sc., Fellow of the Royal Faculty of Physicians and Surgeons, Glasgow; of the Inner Temple, Barrister-at-Law, etc., Regius Professor of Forensic Medicine, University of Glasgow; formerly Professor of Forensic Medicine, University of Egypt, Cairo; and Medico-Legal Consultant to the Egyptian Government. Pp. 671; 132 illustrations. Seventh Edition. Baltimore: The Williams & Wilkins Company, 1942. Price, $8.00.

Clinical Laboratory Diagnosis. By SAMUEL A. LEVINSON, M.D., Director of Laboratories and Pathologist, Research and Educational Hospitals, Chicago, Ill.; Professor of Pathology and Assistant Professor of Medicine, University of Illinois College of Medicine; and ROBERT P. MACFATE, CH.E., M.S., PH.D.; Assistant Director of Laboratories, Research and Educational Hospitals, Chicago, Ill.; Assistant Professor of Pathology, University of Illinois College of Medicine. Pp. 980; 156 illustrations, 15 plates (7 in color). Second Edition. Philadelphia: Lea & Febiger, 1943. Price, $10.00.

Obstetrical Practice. By ALFRED C. BECK, M.D., Professor of Obstetrics and Gynecology, Long Island College of Medicine; Obstetrician and Gynecologist-in-Chief, Long Island College Hospital, Brooklyn. Pp. 938; 1064 figures. Third Edition. Baltimore: The Williams & Wilkins Company, 1942. Price, $7.00.

This volume needs no introduction to teachers of obstetrics. The section on operative obstetrics has been completely revised and rewritten. The number of illustrations has been increased and some are in color. The volume is characterized chiefly by its numerous and excellent illustrations, especially those which deal with the mechanism of labor. Since its second edition appeared, one has been published in Portugese. It is supplied with an unusually full index. For the practitioner the volume may be considered somewhat elementary, but for the medical student, anxious to grasp the subject with the least effort, it would seem that there could be no better choice. D. M.

Diseases of the Skin. By OLIVER S. ORMSBY, M.D., Rush Professor of Dermatology, University of Illinois; Attending Dermatologist to the Presbyterian Hospital of Chicago; and HAMILTON MONTGOMERY, M.D., M.S., Associate Professor of Dermatology and Syphilology, Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota. Pp. 1360; 654 figures (6 colored plates). Sixth Edition. Philadelphia, Lea & Febiger, 1943. Price, $14.00.

PROGRESS
OF
MEDICAL SCIENCE

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF
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THE SURGICAL TREATMENT OF OTOSCLEROSIS

WITHIN the past few years the otologic world has become deeply interested in the surgical treatment of otosclerosis. The fact that the medical treatment of otosclerosis gave disappointing results stimulated a few intrepid surgeons to work on the problem of the surgical relief of otosclerosis. The early pioneers believed that they obtained an instantaneous improvement in hearing as soon as a fistula into the labyrinth was established. This was first observed in 1876 when Kessel extracted the ankylosed stapes and again in 1897 when Passow made a sound-fistula into the promontory with a trephine. There was little improvement in hearing, however, and it lasted but a few days.

General opposition to the operations arose, for they were regarded as dangerous to the hearing as well as to the life of the patient. For 10 years the problem slumbered, to be revived by Bárány who made a sound-fistula into the posterior vertical canal; but again, the improvement in hearing lasted but a few days. In 1913 Jenkins made a fistula into the horizontal canal and obtained immediate improvement in hearing in 2 cases of otosclerosis, but when one of the patients soon became completely deaf and the other lost the improved hearing, he abandoned the operation. Four years later Holmgren made a fistula on the upper curve of the anterior vertical canal, exposing this to the dura, and the immediate result was good but of brief duration. At this time Bárány made a fistula into the horizontal canal and covered it with a pad of fat previously transplanted into the mastoid cavity; an improvement in hearing was observed for 14 days. In 1920 Holmgren, employing magnifying optical instruments, made an opening into the promontory which he covered with mucoperiosteum, but again the result was only temporary. Two years later he utilized the same technique on the horizontal semicircular canal, with permanent improvement in hearing in some cases, although the improvement was never great. In 1924 Sourdille began working on the problem, and encouraged by his enthusiasm, results and technical skill, Holmgren further refined his technique. He exposed the saccus endolymphaticus and made a fistula into the horizontal and vertical semicircular canals. A prosthesis

of fat was placed over the fistula, the inner antrum wall having first been covered with gold leaf to prevent adhesion to the membranous labyrinth. In 1936 Holmgren[7] described 34 patients who had been operated upon with different modifications of this technique. There were no serious complications and no deaths; tinnitus disappeared entirely or almost entirely, vertigo within a month, and the improvement in hearing was constant and surprising.

The technique of the modern exponents of the surgical approach to the otosclerosis problem was adapted and elaborated upon with considerable skill by Lempert.[9a] He describes a procedure designed to create a fenestra in the bony capsule of the external semicircular canal and to provide a mechanical means of keeping the fenestra permanently open. Success depends on skilful and patient execution of a number of orderly surgical steps and its technique should not be attempted by any but otologists who have been specially trained to perform difficult surgical measures of this type. Indications for the operation are: clinical evidence of fixation of the stapes; loss of hearing by air conduction of not more than 60% (if practical improvement in hearing sufficient to permit the patient to resume his economic and social life is to be obtained); loss of hearing by air conduction of not less than 40%, when accompanied with a loss of practical hearing; normal hearing by bone conduction determined by masking or a loss in hearing by bone conduction, determined by masking, which does not exceed 30 decibels for the 512, 1024 and 2048 frequencies; complete absence of suppuration from the middle ear; completely normal and translucent membrana tympani without perforations; completely intact and healthy cutaneous lining of the bony wall of the external auditory canal; and a normal state of health. The endaural, antauricular approach to the temporal bone is employed because of the following reasons: the tympanomeatal cutaneous membrane can be obtained only when this approach to the temporal bone is used. To avoid risk of postoperative infection, in addition to applying the strictest rules of asepsis, the surgical attack must be limited to the tissues directly concerned and thus reach the objective with the least amount of sacrifice of tissue. Better visibility and accessibility of the desired surgical field are obtained by this approach. Lempert operated on 23 patients and in 19 good practical improvement in hearing was obtained and maintained; in 4 in whom the operation was performed despite poor existing bone conduction, no improvement in hearing was secured. The new fistula in the external semicircular canal remained open in 22 patients.

In 1940 Lempert[9b] reviewed his results in 120 cases in which the operation was performed by means of his one-stage technique. The essentials of this technique are: creation of a new window in the horizontal semicircular canal to replace the occluded oval window, and reconstruction of the tympanic cavity to include within it this new window by: *a*, creation of an intact continuous membrane of the skin of the external canal, Shrapnell's membrane and the drum membrane; *b*, amputation of the head and neck of the malleus, to permit Shrapnell's membrane to be pulled back to cover the new window; *c*, preservation of the incus in its normal position; *d*, removal of the pyramidal eminence to widen the tympanic cavity; and, *e*, closing the tympanic

cavity from the outer ear with the tympanomeatal membrane so as to include the new window in the tympanic cavity. In the series of 120 cases, restoration of practical physiologic hearing occurred in 69 cases, marked improvement in conversational hearing in 10 individuals, no improvement in 27, and further loss of hearing in 14 cases. Tinnitus was completely relieved in 69 patients and was diminished in 10. In 100 of the 120 cases the new window remained open; in 31, revisions were done. In commenting on Lempert's work, Shambaugh[13a] states that Lempert is criticized, partly by those who have not taken the trouble to investigate and observe his work and who have perhaps seen one or two poor results, since patients with poor results are more prone to seek help from other physicians than are those with good results. Others criticize Lempert because of his enthusiasm for his operation. For example, he uses the term "permanent improvement" when one cannot yet be sure of the ultimate fate of the hearing in the cases in which his technique has been used, since insufficient time has elapsed. Exception can also be taken to certain statements, *i. e.*, that Shrapnell's membrane reaches and covers the fistula and that infection of the outer middle or inner ear was never encountered. Shambaugh believes that a slight low-grade infection of the postoperative cavity must be a common occurrence and that Shrapnell's membrane does not cover the fistula. His experience with tinnitus has been less favorable. In some patients with excellent and sustained hearing improvement the tinnitus has recurred, and in others it has not been relieved. In other respects his experiences with the fenestration operation are similar to those of Lempert. From his experiences Campbell[1] believes permanent improvement of hearing in cases of chronic progressive deafness by fistulization of the labyrinth depends on maintenance of the fistula by prevention of bony regeneration of the labyrinthine wall. He reports on 8 cases in which fistulization was performed according to the technique described by Lempert. In 4, considerable improvement of hearing was shown by audiometric examination. In 2, hearing in the ear operated on had been made worse, and in the remaining 2 there was little or no change in hearing. Passe[11] operated on 14 patients and finds that within 18 months following the procedure it is difficult to assess the real value of the operation. Though hearing showed improvement in 5 patients, only 3 have improved to an appreciable extent for conversation. In all but 5 cases hearing loss progressed after operation, but this loss was always more evident in the unoperated ear than in the operated ear. In all improved cases the fistula sign was present. In the absence of other treatment, Passe believes that these results justify continuance of efforts to produce a permanent opening in the bony canal. The indications for fistulization of the labyrinth are reviewed by Canfield[2] who presents 3 cases, 1 of a patient considered suitable for operation and 2 regarded as unsuitable. Of the latter, 1 had headaches of long-standing duration and undetermined origin, and the other had a healed cavity following radical mastoidectomy for chronic suppurative otitis media. The 2 unsuitable patients showed no improvement in hearing. The suitable patient showed an average gain of 15 decibels for the 3 conversational frequencies 1 month after operation.

In the opinion of Fowler[4a] fenestration of the labyrinth is the one

surgical technique which appears promising for the alleviation of conduction deafness. On the basis of experimental work by himself and others he discusses the causes of closure of labyrinthine fistulas. The first factor is bone chips which act as foci from which new bone growth takes place. Second, it has been found that the enchondral bone of the labyrinthine capsule does not participate in the bony healing of fractures. Consequently, the fistula should be made in the solid angle where the enchondral capsule is relatively thick and the periosteal capsule is relatively thin. Third, a larger fistula is apparently less likely to close. Fourth, infection undoubtedly tends to increase bone regeneration. Finally, he expresses the belief that fistulization is as dangerous as any major surgical procedure on the mastoid, perhaps more so. Goodyear[5] describes a simplification of the Lempert fenestration technique in which the conventional postauricular approach is employed. The operation was used on a patient who showed a positive reaction to the fistula test $3\frac{1}{2}$ months after operation. Utilizing the postauricular approach, Porta[12] makes a fistula into the horizontal semicircular canal, exposing the membranous canal widely and covering the fistula with a portion of the aponeurosis of the temporal muscle. An opening is then made into the external auditory meatus to this aponeurosis. The middle ear remains unopened. Because the fistula in the labyrinth frequently closes, improvement in hearing is often transient. Nasiell[10] states that it is impossible to separate otosclerosis from chronic adhesive deafness, an artificial fistula being of equal importance in both diseases. Hughson[8a] describes the indications for his round window graft operation for deafness. It is a procedure unsuitable for patients with hearing losses below the general level of 50 decibels, and should not be performed on patients over 50 years. Hughson and Witting[8b] state that in view of the expected range of variation no change in the hearing level of any frequency less than 10 decibels can be considered of consequence. Because the 5-year cure has become more or less a standard for determining a satisfactory end-result in the majority of pathologic conditions, they maintain that a patient should have the assurance of retaining any gain obtained for at least this length of time. After presenting his results with his round window graft operation in a series of 30 patients operated on over a 3-year period, Hughson[8c] concludes that his statistical analysis indicates a trend toward improvement in the patients on whom he operated. Subjective improvement was experienced by 60% of all the patients and by 85% of those with favorable results. Tinnitus was alleviated in 5 out of 15 patients, and in 1 patient it was worse. As a result of this surgical procedure in no patient was the hearing impaired.

Guggenheim and Guggenheim[6] criticize the fenestration operation on three grounds. They state that the proponents of the fistula operation do not recognize the fact that otosclerosis is not only an osseous dystrophy producing an obstruction to sound conduction but that it is also a disease of the eighth nerve producing perception deafness, so that even though a fistula operation should prove successful, it could in no way inhibit further deterioration of the neural mechanism. They believe that medical treatment of otosclerosis through dietary regulation and the administration of calcium, phosphorus and vitamins has

produced improvement in hearing far greater than any fistula operation thus far reported. Finally, they maintain that the ingenious, difficult and time-consuming technique which has produced coast-to-coast enthusiasm has nothing whatever to do with the success or failure of the fistula operation. In an osseous fistula produced on rabbits, there was, after 18 days, lively and widespread new bone formation when the fistula was made with a sharp instrument or with a burnishing burr. No evidence of osteogenesis is detected at this time when the use of the burnishing burr has been followed by osteodesiccation by means of electrocoagulation. At the end of some 2 months, all osteoblastic activity has ceased and all mesenchyme has been replaced either by fatty marrow with islands of blood-forming cells or by fibrous marrow. The most patent fistula results from the use of a sharp instrument. Next came the fistula made with the burnishing burr and completed by electrocoagulation, while that made with the burnishing burr alone showed the largest amount of new bone formation. The fact that these operations were performed on a type of bone different from that of the labyrinthine capsule in no way affects the experiments, since all new bone formation is by the membrane-bone process. Shambaugh[13b] takes issue with certain statements made by the Guggenheims relative to the fenestration operation for otosclerosis, namely that greater improvements have been secured by dietary management and that the difficult surgical technique has nothing to do with the end-results of the operation. Pointing out that no treatment for deafness can be regarded as of proved value until audiometrically substantiated and sustained hearing improvements of more than 10 decibels for the conversational frequencies are reported and that such improvements have never been reported following any medical or surgical treatment except for the fenestration operation, the author then presents his results in 31 cases of otoslcerosis in which he operated by Lempert's fenestration technique. Of the 31 patients, 77% showed an audiometric improvement of more than 10 decibels for the conversational frequencies 3 weeks to 14 months after operation.

Ersner and Myers[3a] find that the heat created by the dull dental burr during labyrinthine fenestration does not inhibit osteogenesis. It is believed that it is not the mechanics of the formation of a fenestra that baffles the otologist but the osteogenesis and closure of the fenestra that continue to present the perplexing problem. There is a macroscopic difference in the appearance of the bone after the fenestra is formed by the Holmgren method as compared with that of Lempert. The scraping method of the former leaves the bone dull, and the burring method of the latter leaves it shiny. Experimental work on cadavers and cats showed that the amount of heat produced in the bone by dental drills is slight. They conclude that although the difficulties attending the surgical treatment of otosclerosis have been overcome, the improvement of hearing of patients is only temporary in most cases. In another communication, Ersner and Myers[3b] state that it is impossible to tell beforehand who will and who will not be benefited by the operative procedure. Despite care in determining that bone conduction was good, that evidence of neural involvement was lacking, that the labyrinth functioned normally and that hearing by air conduction was not

lost to the extent of more than 70 decibels, end-results have not been as good as the authors hoped to achieve. With regard to end-results, mere numerical improvement in decibels is of little value unless it brings the patient's hearing within conversational range. Unless this is achieved the operation must be considered a failure. According to Fowler,[4a] recent reports are particularly open to criticism because of their optimistic conclusions and the paucity of facts supporting these conclusions. Outside of surgical methods for combating infection in the middle ear, there is only one surgical technique, fenestration of the perilymphatic labyrinth, which appears promising for alleviation of conduction deafness. Up to the time the article was written, reports complete enough to analyze show that in less than one-third of the cases in which operation was done satisfactory improvement was maintained for more than 6 months. To be legitimate, the minimum requirement for any elective operation for deafness should be an average improvement of at least 15 decibels for the speech range and a permanent reduction in hearing to 30 decibels or less. Elsewhere, Fowler[4b] describes his experiences with closure of operative fenestras in the labyrinth.

A new oval window for improvement of hearing in cases of otosclerosis is described by Lempert.[9c] After the performance of 375 fenestration operations and observation of the end-results, Lempert is convinced that fenestration of the labyrinth is indicated only when air conduction deafness has resulted from stapedial fixation and degeneration of the cochlear nerve has not yet produced impairment of the conversational frequencies, 512, 1024 and 2048. Desirable late end-results can be obtained in such cases only if there are normal and completely intact drum membranes, patent Eustachian tubes, and complete absence of middle ear infection. In 88 of 300 instances in which the external semicircular canal was fenestrated, the newly created fenestra eventually closed partially or completely. There was a period of 2 to 5 months before operation and closure. His study shows that a positive fistula test following fenestration indicates patency of the fenestra only when improvement in hearing continues. In cases of incomplete closure, the minute opening in the region of the ampulla may give a positive fistula reaction but is not sufficient to permit mobilization of the perilymph by air-borne sound and result in improved hearing. After covering the newly created fenestra with the tympanomeatal membrane in 50 cases, Lempert lifted the membrane and uncovered the fenestra after a 10-minute interval. Blood had entered the perilymph space and formed a fibrinous film in every case. This led him to consider the creation of a fenestra: first, in that part of the vestibular labyrinth which has the largest circumference of perilymph space and, second, in a position anterior to the ampulla of the external semicircular canal instead of posterior to it. Thus the fenestra would be nearer Shrapnell's membrane, which makes certain that Shrapnell's membrane always completely covers it. Accordingly, such a fenestra should be an unfavorable site for organization and conversion of a small accumulation of blood in the perilymph space into fibrous connective tissue, and thus its closure by bony metaplasia of a connective tissue mass should be prevented. In order to meet these requirements, the dome of the vestibule was chosen as the most suitable and advantageous

place for the creation of a new labyrinthine fenestra. The fenestra nov-ovalis was established in 75 cases in none of which did signs of impending closure of the fenestra exist at the time of the report. The comparatively large dimensions of the perilymphatic space in the region of the fenestra nov-ovalis offer an opportunity for inserting and permanently maintaining in direct contact with the lateral bony walls of the fenestra, an inert metal obturator frame (platinum and iridium) for mechanical prevention of closing of the fenestra. The observations indicate that fenestra nov-ovalis is anatomically well placed, histologically well constructed, and physiologically has a good functioning hearing window conceived and used to replace a functionally impeded fenestra ovalis. Like the fenestra ovalis, the fenestra nov-ovalis communicates directly with the scala vestibuli. Like the fenestra rotunda, it is covered by the thinnest possible membrane, both the inner and outer surface of which are lined with epithelium. According to Shambaugh,[13c] the comparative merits of different surgical techniques for improving hearing in otosclerosis can be determined only by a comparison of the hearing results. The minimum data necessary for evaluation and comparison of results should include the following features: every operated case should be reported; hearing should be measured audiometrically; there should be adequate controls, the unoperated ear being the best control; at least 6 months should elapse before regarding a hearing result after fenestration as probably permanent; and all complications and untoward results, including dead labyrinthitis, should be recorded. All reports of the result of therapy for deafness should present these data. A comparative analysis of the results with four different surgical techniques for improving the hearing in otosclerosis showed that the original Lempert fenestration technique yielded a lasting significant hearing improvement in 27% of cases. The addition of constant irrigation to the technique resulted in a lasting significant hearing improvement in 76% of cases. The further addition of the binocular dissecting microscope to the technique resulted in a lasting hearing gain in 78% of cases. The nov-ovalis technique with irrigation and the microscope yielded a hearing gain in 88% of cases that have been tested 6 months or longer after operation.

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DERMATOLOGY AND SYPHILOLOGY

UNDER THE CHARGE OF

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PINTA—A REVIEW OF RECENT ETIOLOGIC AND CLINICAL STUDIES

WE have a fourfold purpose in reviewing the newer developments in the knowledge of pinta. Although there are several excellent reviews in English by Sáenz, Grau Triana and Alfonso Armenteros,[68a] by Pardo-Castello and Ferrer[60] and by Holcomb[40] and numerous papers by various Latin Americans and a monograph by León y Blanco,[49ff] these accounts are not readily accessible to the majority of the medical public. Pinta deserves special attention and repeated emphasis at this time because of the numbers of military personnel who are stationed, or will be, in the tropics. Certainly after the war it may be expected that cases of it will turn up in this country. Furthermore, it is a medical condition involving large numbers of people and recent years have added much to our understanding of its etiologic and clinical background. Finally, pinta is of great theoretical interest in that the recently discovered spirochetal (treponemal) cause for it further complicates the question of treponematosis by adding still another diseased state which has to be given a proper nosologic interpretation. It is our purpose, therefore, to discuss briefly the possible relation of pinta to other treponematoses and to present the data which comprise the present knowledge of the condition.

The Treponematoses. Although our experience has suggested the possibility of the existence of strains of *Spirochæta pallida* with individual biologic characteristics (*e. g.*, treatment resistant[7,8]), we are not proposing to discuss the treponematoses from the partisan viewpoint and side either with the unitarians or the dualists. For the sake of better understanding of pinta, however, a brief résumé of the arguments for and against the unitarian viewpoint is desirable. For a complete recent review of the subject the reader is referred to Goodman,[32] Stannus,[71] Blacklock,[11] Butler,[15] Williams,[79] Fox,[26f] Turner and associates (Ferris and Kumm[24,45,75]), Hudson,[41] Pardo-Castello,[59b] Hoffman,[39] Hasselman[37] and others. Hudson (personal communication, as yet unpublished) has defined the treponematosis as, "a universally distributed acute and chronic specific disease, known in various times and places by a large number of names, such as syphilis, yaws, pinta, bubas, button scurvy, morbus gallicus, bejel, morfea, pian, irkintji, franghi, mentagra, carate, frambesia, venereal leprosy, sibbens, empeynes, radesyge, and many others. It is caused by a treponema, and is propagated both venereally and non-venereally. It is susceptible to treatment with the heavy metals, is diagnosed by special tests, is characterized by an early and late stage separated by a latent period,

and it evokes a characteristic pathological response from human tissues."

The precise relationship of the individual members of this group to each other has not been definitely determined and for a number of generations physicians have claimed sufficient differences both clinical and epidemiologic for many of them to distinguish them by separate names. Others have presented clinical material which demonstrates that the differences are not real (mucous membrane lesions occur in yaws;[36] and bejel;[41h] nervous system lesions are found in bejel;[38] bone lesions in yaws and in bejel;[65,79] palmar and plantar lesions in bejel and in pinta, especially in the Cuban cases;[41e,68a] juxta-articular nodules in bejel;[41d] visceral and aortic changes in yaws and in pinta;[78] depigmentation in bejel,[41e] as well as in pinta.)[49ee] The chief point of discussion is whether the dissimilarities claimed for the various members of the group are due to variations in the host or his environment or to inherent biologic differences in the infecting organisms. The immunologic relations between the conditions are not clear. Hudson, from his extensive study of bejel, believes that environmental factors (climate, sociologic, economic, religious, and medical) play a great rôle in determining whether the disease is transmitted venereally (syphilis) or non-venereally (bejel). On the other hand, while the dualists believe that there are biologic differences among the causative organisms of the treponematoses, they admit that perhaps in the remote past they were identical, but that there is no good evidence to indicate that differentiation occurred within historic times. Blacklock[11] and others (Hudson) have clearly pointed out that those who claim syphilis and yaws (also bejel and pinta) are different diseases are comparing a non-venereal disease of children (bejel) or of rural areas of the tropics (yaws) with adult venereal syphilis.

Definition. Pinta is a chronic endemic disease of long duration, infectious, possibly contagious or transmissible by an as yet unknown vector. It is characterized by papular or papule-like initial lesions and is followed in a variable but usually long time by an erythematosquamous eruption which increases continuously and is transformed into dermatitic plaques which are superficial atrophic, pigmented and achromic, accompanied frequently by palmar or plantar keratodermias, and enlargement of superficial lymph nodes. It is now supposed to be due to a specific treponema. The cutaneous lesions are at times accompanied by visceral changes (aorta, nervous system).

Synonyms for Pinta. Pinta has been known by a variety of names according to the locality in which it is described. Pinta resembles yaws and bejel in the multiplicity of designations used among native peoples for it. Long lists of recent and older local designations for the syndrome are given by Brumpt,[14b,c] by Holcomb,[40] and by León y Blanco.[49ff] The name, pinta, or *mal del pinto*, is said to have originated in Mexico and one of the first to use this name was the American physician, Samuel M'Clellan[58] in 1825. Among the more commonly used names are *Tiña*, *Mal del Pinto* (Mexico), *Carate* (Colombia), *Azul* (Chile, Peru), *Boussarole* (Haiti), *Guasarola* (Dominican Republic), *Purú-purú* (Brazil), and *Cativi* (Guatemala).

History. León y Blanco[49dd,ee,ff] reported an extensive study of the historical development of the knowledge of pinta. This full account

has been supplemented by contributions dealing with special aspects (Pequeño,[62b,c] Holcomb,[40] González Herrejón *et al.*,[30,31] and Sáenz, Grau Triana and Alfonso Armenteros[68a]). Beginning with the report of Alzate y Ramírez,[1] the subsequent story of the sequence of events leading to the present concept of the syndrome is full of information which foreshadowed much that is now considered new. The reader is referred to the original studies for details but certain recent developments must be outlined. Little attention was paid to pinta until Ruiz Sandoval[66] and Montoya y Flores[56] described certain phases of it and expounded the parasitic theory, and considered a number of Aspergilli and Penicillia as the cause. For about 25 years subsequently, it was considered as a more or less rare tropical disease. The recent history of pinta has been divided by Sáenz and his associates[68a] into three periods. The first period extended from 1921 to 1929 during which time the condition was considered to be a special type of late keratotic syphiloderma of the palms and soles. The second commenced in 1929, when this condition was presumably identified as carate, an advancement in which Dr. Howard Fox[26] of New York, and Peña Chavarria and Shipley,[61] played a prominent part. The third period began August 3, 1938, with the discovery of the spirochete which causes the condition, in dyschromic lesions and lymph nodes, and with the confirmation of the hypothesis previously held by certain investigators as to the spirochetic nature of the disease.[26,31,54]

Geographic Distribution. *Frequency of Occurrence.* Pinta is almost entirely American in distribution. It affects chiefly dark-skinned peoples and is endemic in Colombia and Mexico. It also occurs in Venezuela, Cuba,[35,59a,60,68a] Brazil,[70] Ecuador,[22,48] Peru, Bolivia, Guiana, Honduras, Argentine, Nicauragua, Puerto Rico,[16] Haiti,[3] Santo Domingo, Virgin Islands,[26h] Guadeloupe, San Salvador,[5,61] and Central America (Panama). The Puerto Rican cases are said to occur in immigrants from Colombia. No cases apparently have been reported from Uruguay. Fox[26e] could not confirm the reports that white pinta or vitiligo existed in Yucatan.

Cases of pinta have been reported from other parts of the world. Africa,[10] Egypt,[52] Algiers,[33] Sahara,[43] east of Tripoli,[47] Turkestan, Philippine Islands,[80] and Turkish Isles in the South Pacific. Cases have also been reported from Iraq and among the dark-skinned races of India,[21,51] and the Straits Settlements.[21,51] Fernandos[23] and DeSilva[20] reported on pinta occurring in Ceylon. Fox[26d] claimed that the case reported as pinta by DeSilva[20] was unproven.

About 1,000,000 persons in Latin America are affected by pinta. Of this number about 300,000 cases are in Mexico, 600,000 are in Colombia. Iriarte[44] estimated that there were about 400,000 cases in Colombia, and about 55,000 cases in Venezuela. In Cuba where so much advancement in the knowledge of the disease has occurred, there are only about 200 cases.[49ff] In Ecuador, there are approximately 5700 cases.

In Mexico, a commission found in 1929–31, 11% of 2,500,000 people examined were affected by the disease. The disease is endemic in approximately the southern half of the Republic. The greatest number of cases were observed in the State of Guerrero, 23.67% of the population of more than 500,000 being affected. Other states in which the disease was most prevalent were in order of frequency, Oaxaca, Mexico,

Michoacan, Puebla and Chiapas. In certain municipalities of the state of Barinas in Venezuela more than 50% of the inhabitants are affected and for the entire state the incidence is not less than 10%.[13] Peña Chavarría and Shipley[61] estimated that about 6.8% of the inhabitants of Colombia have the disease. León y Blanco[49ff] cites other available data on the incidence of pinta.

Etiology. *Discovery of the Spirochetal (Treponemal) Cause of Pinta.* For about 45 years a parasitic cause was surmised for pinta. At one time, a bacillus was thought to be involved.[28] A mycotic origin was suggested by some of the earlier writers,[4,56,66,67] and as late as 1936 Brumpt[14a] listed 27 species of fungi reported to be the cause according to various authors. In 1889, Téllez[73] for the first time recorded the idea that pinta is an exanthematic form of syphilis and is transmitted by venereal contact. Although a number of investigators had failed to be satisfied with the mycotic origin of the disease,[2,17,25,26] and in spite of the report of Gratz[35] and of Soberón y Parra[69] of the curative action of neosalvarsan, the possibility of a spirochetal cause of pinta was not given much consideration until the work of Menk[54] and González Herrejón.[30] Menk, of the United Fruit Company, studied 67 patients with carate in the Hospital Santa Marta in Colombia and found that 74.5% of them had a positive Wassermann reaction. He believed that these results indicated that carate is in some way related to an old treponematosis and that at least there is an association of etiologic factors such as a treponematosis and mycosis occurring at the same time. In 1927 González Herrejón came independently to the conclusion, after the intensive study of 3 cases, that pinta was not a mycosis but a spirochetosis related to syphilis and yaws. González Herrejón and Pallares[31] found positive serologic reactions in nearly 100% of the patients suffering from pinta in Mexico, and were unable to isolate pathogenic fungi from the affected skin. Fox, in 1928[26a] and 1930,[26c] was unable to obtain pathogenic fungi from the skin of pinta patients and agreed with González Herrejón that the disease was a spirochetosis. In 1930 Thonnard-Neumann[74] and associates found 90% positive Wassermann reactions in their 75 cases. They also found positive cerebrospinal fluids in 2 of 5 cases and changes in the aorta, demonstrable roentgenologically, in 80% of the cases. Pardo-Castello in 1936[59a] reported a number of cases of pinta from Cuba and affirmed the spirochetal nature of the disease in conformity with González Herrejón and Fox. Mooser, Varela and Vargas[57] did not find any organisms in the scrapings from lesions and the blood of Mexican patients with pinta and attempts to transmit the infection were unsuccessful. The positive proof of the spirochetal nature of pinta was developed when, on August 3, 1938, Drs. Grau Triana and Alfonso Armenteros, on the service of Prof. Braulio Sáenz, found a spirochete in the lymph of the dyschromic cutaneous lesions of a Cuban case of pinta. This spirochete was undistinguishable from that of syphilis and yaws. León y Blanco[49] found the organisms in the lymph nodes (juice of lymph node obtained by "gland puncture" and by Levaditi stain in sections. These findings were confirmed by Pardo-Castello[60] two days later in a case of his own in the dermatologic service of the Hospital Calixto Gorcía. Because of the scarcity of cases in Cuba, León y Blanco was sent to Mexico where he made a number of important

studies which have changed the entire clinical concept of the disease. He demonstrated that the treponemas were present constantly in the cutaneous manifestations of the disease and absent in healthy persons. He also produced the disease experimentally in man, studied pintagenous zones in Mexico, established the course of the disease and various factors concerned with its epidemiology. His studies have been confirmed by various investigators in several of the Latin American countries.[13,16,22,27,30,48,76]

The Spirochete (Treponeme). Various authorities have described the organism, presumably responsible for pinta. It has been variously called *Treponema carateum* (Brumpt), *Treponema herrejoni* (León y Blanco), *Treponema pictor* (Grau-Alfonso) (Pardo-Castello[59a,c]), *Treponema americana* (Briceño Rossi and Iriarte), *Treponema discromoderma* (Leon), *Treponema pintæ* (Sáenz, Grau Triana, and Alfonso Armenteros). It has been found in serum from keratotic lesions,[49c,aa] in biopsy material from the skin lesions, especially the erythematosquamous lesions ("empeines" or "jiotes" as they are called in Mexico). León y Blanco[49aa] found the organism 254 times in 254 cases examined. They were first found in dyschromic and hyperkeratotic lesions of the hands and feet, typical of Cuban pinta.[68a] In late lesions, the spirochetal findings are variable. Pardo-Castello and Ferrer[60] found them to be as rich in spirochetes as the early ones, but the active edges are usually more so. The atrophic areas ("burnt-out process") are usually free of spirochetes. The organism is morphologically indistinguishable from *Spirochæta pallida* and, except for minor variations, the description of León y Blanco[49f] is widely accepted:

Dimensions of the organism. "The length varies greatly between 7.8 and 36.8 micra; it has been calculated an average value of 17.8 micra from 500 measurements, ranging in length from 12–18 micra ordinarily. It is from 0.25 to 0.30 micron thick and its spires are from 0.8 to 1 micron in depth, measuring the size of each interval of the screw 1 micron. The number of spires changes according to the length of the particular specimen observed.

"By darkfield examination it looks like a cylindrical filament rolled up around a fictitious longitudinal axis in the form of a helix or screw, the spires of which being very regular and close. Such spires appear rigid at rest, but they contract and relax constantly along the longitudinal axis of the screw whenever the germ moves. Its ends are sharp-pointed.

"The motility of *T. herrejoni* holds a very close resemblance with the motility of *T. pallidum*, showing as high a rate as that of the latter. It turns rapidly around its longitudinal axis and may exhibit an O, P, or S-shaped form after bending itself by distortion or flexion movements. Undulating or creeping movements are not infrequently shown by the whole body of this parasite.

"It is readily stained by the silver impregnation methods advised for staining Spirochetes in smear preparations, as well as by Giemsa's stain, Carbolfuchsin, and Gentian Violet, after picric acid, tannin or Potassium permanganate has acted upon the smear.

"A 10% solution of Saponin dissolves these Treponemata in 6 hours at room temperature. The same result is obtained either by sodium taurocholate or bile. Distilled water causes them to swell."

León y Blanco has not yet succeeded in culturing the organism and a suitable animal for inoculation still remains undiscovered.

In fresh preparations the organism remains motile from 1 to 6 hours according to the temperature. Heating the specimen to 50° C. for 15 minutes kills the organisms but at 40° C. and at 42° C. they survive 3 and 1½ hours respectively. Varela and Nieto Roaro[76] found that the organism dies more quickly in bile than does *Spirochæta pallida*.

Curbello, Palomino, Conde and Garzon[19] have cultured biopsy material from pinta lesions in ascitic fluid under aërobic and anaërobic conditions. They were able to produce a spirochetal keratitis by injecting this culture material into the anterior chamber of the eye of a rabbit. León y Blanco[49ff] was unable to confirm these findings.

Transmissibility of Pinta. Attempts to inoculate guinea pigs, rabbits and rats with pinta have failed.[77] Sáenz[68b] stated without detail, that "the cornea and testicles of rabbits were inoculated with fragments of tissues from persons with pinta, and keratitis and epididymitis similar to those obtained in experimental syphilis resulted." Although Ortiz and Gandara[58] were able to produce keratitis by inoculating serum from skin lesions containing numerous spirochetes, no organisms could be demonstrated in the lesions thus induced. Attempts by the same investigators to produce lesions in parrots and pigeons were also unsuccessful.

In spite of the reported failure of Mooser, Varela and Vargas[57] to produce positive inoculation of healthy men and laboratory animals with the blood and exudates from the lesions of pinta, León y Blanco in 1938[49a] successfully inoculated himself and volunteers with material containing the spirochete of pinta. As a result of these inoculations he has made observations which have clarified the clinical concepts of pinta. This investigator found, incidentally, that syphilis does not render a patient immune to pinta. A superimposed infection cannot be obtained during the pigmentary period of pinta; on the other hand, it is always obtained during the initial or spreading periods of the infection. A first attack does not give rise to immunity. A short time after recovery from the first attack (2 months after recovery from the disease in the primary period or 4 years in the dyschromic one, approximately) it is possible to produce experimental reinfection.

Aside from direct inoculation of infected material from a diseased to a healthy person, pinta is thought to be carried to the new host by way of an insect vector. This idea has been entertained for a long time. León y Blanco and Soberón y Parra[50] fed the fly *Moscas Hippelates* with serum containing *Treponema herrejoni* and succeeded in transmitting the disease by placing the flies to feed immediately afterward on cutaneous excoriations of a volunteer. León y Blanco[49b] also found the treponemata of pinta in bed-bugs (*Cimex lectularius*). He believed that if the insect vector is involved, it might transmit the disease by depositing upon the abraded skin its feces containing the spirochete or by being crushed upon abraded skin at the time of biting.

The histologic changes in the cutaneous lesions and the lymph nodes in pinta have been fully described by León y Blanco.[49g] The initial lesion and pintids show slightly thickened epidermis with elongation of the papillary processes. The stratum mucosum presents edema and intercellular infiltration of lymphocytes. The pigment is scarce in the basal layer. The corium shows a dense perivascular infiltrate of plasma cells, lymphocytes and occasional histiocytes and polymorphonuclear

leukocytes. There are numerous melanophores in the papillary layer. The endothelium of the blood-vessels are invaded and sometimes dissociated by the inflammatory cells. The pigmentary changes reflected by the blue-black or brown of the lesions are already noted in the histology of the early lesions.

The late lesions show "atrophy of the epidermis, absence of pigment in the basal layer, huge accumulation of melanophores in the upper part of the corium, alternate or continuous band-like infiltration of lymphocytes in the papillary and subpapillary layers, and, in cases in which the hyperkeratosis is a decided feature, the accumulation of corneous material on the atrophied epidermis."[60]

In all cases studied by Pardo-Castello and Ferrer, "atrophy of the epidermis has been an almost constant feature and the patches of melanophores in the subpapillary region a characteristic histopathologic observation. Extracellular grains of pigment may also be noted in and between the cells of the infiltrate. In the leukodermic patches, there is complete absence of pigment, atrophy of the epidermis, disappearance of the papillæ and sclerosis of the connective tissue. These are evidently the end of the inflammatory process and represent the final stage, atrophic and cicatricial, of the disease. However, León y Blanco[49ff] reported on some early vitiligoid lesions with active inflammation in which spirochetes are particularly abundant." Pardo-Castello and Ferrer[60] have been able to confirm this observation in a case of vitiligo-like lesions of the scrotum. Becker[6] considered the depigmented spots of pinta as an end-stage, and hence its lack of response to treatment. In all lesions of pinta it is possible to demonstrate spirochetes among the cells of the epidermis, especially in the stratum Malpighii by silver impregnation methods.

Sáenz, Grau, Triana and Alfonso Armenteros[68] have described the essential pathologic features of keratosis. The chief epidermal change is marked hyperkeratosis. Otherwise the findings are essentially as outlined above.

León y Blanco[49c] in his discussion of lymph node pathology noted that all are affected by chronic adenitis very much like that of syphilitic lymph nodes. The process terminates in a perivascular sclerosis and on spreading destroys almost all the parenchyma. Two features distinguishing pinta lymph nodes from syphilitic lymph nodes are the constant presence of melanin pigment and some hyaline corpuscles the nature and significance of which are as yet undetermined.

Eosinophilia. In 1925 Peña Chavarría and Shipley[61] called attention to the occurrence of eosinophilia (10% to 73%) in pinta in patients free from intestinal parasites. These results were confirmed by González Herrejón (1927)[31] and others. Eosinophilia occurs in about 75% of cases. León y Blanco also observed increase in basophils in 10% of cases. Local eosinophilia also occurs in the cutaneous lesions and enlarged lymph nodes of pinta.[49bb]

Serology of Pinta. Two facts have been disclosed by numerous studies which indicate the relationship of pinta to syphilis. They are the blood-serologic findings and the response of pinta lesions to antisyphilitic remedies. The outcome of the blood tests and the results of treatment are well known to syphilologists to be highly non-specific in nature.[72] Nonetheless they have played a prominent rôle in the

development of the spirochetal theory of etiology of pinta and will be briefly reviewed. The serologic tests are still of value in diagnosis, if not differential diagnosis, and the antisyphilitic therapy offers hope for control of the disease, pinta.

The blood serologic tests, both complement fixation and flocculation, have given variable but uniformly high percentages of positive reactions in the various phases of pinta. Pardo-Castello and Ferrer[60] in a summary statement believed the serologic reactions were positive in about 60% of patients with the early stage of the disease. Serologic reactions in the late period of the disease were, according to these investigators, positive in 100% of the cases. The serologic reactions gradually become positive as the disease evolves. Effective treatment usually has no influence on the serologic reactions. This serologic fastness is, according to León y Blanco[49ff] a constant feature of pinta (*secuela serologica*).

The proportion of positive serologic reactions in pinta varies according to the author, the type of test and the phase of pinta considered. Menk[54] found 74.5% positive Wassermann reactions. Register[64] used the Wassermann, Kahn and Meinicke tests. Of 287 patients tested with the Wassermann test, there were 80.6% strongly positive, 4.8% moderately positive, 6.7% negative, and the remainder negative. 117 of those tested with the Kahn test, 81.1% gave positive reactions, 5.6% were weakly positive and 7.6% were negative. The Meinicke test gave 74% of 118 cases positive, 5.4% slightly positive, and 11.4% negative.

Pérez Rodríguez[63] found the Wassermann test strongly positive in 95.5% of 109 cases. Thonnard-Neumann and associates[74] found 90% of 75 cases in Colombia positive. Briceño Rossi and Iriarte[13] in Venezuela found that in two regions the treated cases gave 78% and 77% positive Kahn reactions, while among the untreated cases the percentage of positive Kahn reactions was 100. A Mexican Commission[55] found 125 of 130 cases positive. León in Ecuador found 78% positive to the Wassermann test and 90% positive Kahn reactions. The strength of the flocculation reactions was more intense than the complement fixation reactions. González Guzmán[29] in a series of 3 papers found that with the Wassermann and the Kahn verification tests the blood of pinta patients reacts like the blood of patients with syphilis. The verification test gave the syphilitic type of reaction in 20 patients with late clinical lesions. In patients with "pintides" (early stage) the Kahn test always gave positive reactions but the Wassermann test yielded inconstant reactions, being negative in 30% of the cases. Chargin and Rein[18] tested 268 cases of pinta with the Kahn verification test. All gave positive (4 to 160 units) reactions to the Kahn quantitative test. Of the 225 specimens, 83.9% gave the syphilitic type of verification reaction while 6.3% gave the general biologic (non-syphilitic) type of reaction, and 9.7% gave inconclusive results. These data parallel those of Escobar. Briceño Rossi and Iriarte[13] performed 111 Kahn verification tests in cases cured after 1 year. While the proportion increased to 100% in the active cases, 78% were strongly positive. Recently a new Kahn verification procedure has replaced the heat test. No reports have been found based on the application of this new procedure to pinta blood. Sáenz, Grau Triana and Alfonso Armenteros[68] found persistently positive serologic

reactions in all their cases in spite of treatment. León y Blanco[49g,cc] studied the serologic reactions in various phases of pinta. In the primary period, he found negative reactions in 17 experimentally inoculated patients, at the time of inoculation and just at the start of treatment. In the secondary period, he performed 94 Bordet-Wassermann tests and 107 Kahn tests. While 88.78% of the flocculation tests gave positive reactions, 86.14% of the Bordet-Wassermann tests also gave positive reactions.

The cerebrospinal fluid in pinta has also received considerable attention. The Mexican Commission[55] found meningeal reactions and strongly positive Wassermann reactions. Varela could find no cerebrospinal fluid changes but in 1936 Pardo-Castello[59a] in his study of 23 cases found 5 with increased globulin values and in 1, positive Wassermann and Kahn reactions. In his study with Ferrer, Pardo-Castello[60] reported that in 12 of 23 (52.1%) cases examined there were pathologic changes in the cerebrospinal fluid similar to those found in asymptomatic neurosyphilis. Sáenz and his coworkers[68] found cerebrospinal fluid changes in 10% of the cases. Grau Triana[35] studied the cerebrospinal fluid of 12 patients with pinta and found abnormalities in 2 of them. Botero[12] found no cerebrospinal fluid changes in 69 patients with carate examined. León y Blanco in unpublished work found no abnormalities in the cerebrospinal fluid of 53 patients in the late phase of the period of generalization.

Treatment. The treatment of pinta is similar to that of syphilis and yaws. The details of the development of the knowledge of the value of the major antisyphilitic drugs (arsenicals, mercurials and bismuth compounds) and even fever[49h] are fully covered in the monograph of León y Blanco[49ff] and in Holcomb's[40] review to which the reader is referred for details. Mercury and the arsenicals were used as early as 1913 by Gratz[34] in Colombia. León y Blanco states, however, that the mercury salts were used empirically for more than a century for the treatment of this disease[9] (1811). Although the modern arsenicals for pinta include mapharsen (arsenoxide) we find no reference to the application of massive arsenotherapy to this disease.

Epidemiology. Pinta is essentially a rural or suburban disease, occurring chiefly among individuals of poorer classes, laborers and persons living under unsanitary conditions. Its greatest distribution occurs in river valleys. In certain of the countries, there are distinct "pintogenous" zones. The disease is rare in the white persons. The majority of Cuban patients are negroes, while in Mexico, Venezuela, Colombia and Ecuador persons of the Indian race and mestizos are the most frequent sufferers.[48] Pardo-Castello and Ferrer[60] found the disease in white persons in 12% of their Cuban cases. The disease occurs with equal frequency in males and females (51.52% males and 48.48% females in Mexican group[13,49ff]). It occurs mostly between the ages of 10 to 20 years. The primary lesion occurs especially on the extremities (in exposed parts). The possible mode of transmission is by direct contact, intimate and prolonged. The possibility of an intermediate host (insect vector) has been previously mentioned. Human and animal inoculation has also been dealt with above.

Clinical Manifestations. The extensive studies of León y Blanco in Mexico have led to an entirely new concept of the clinical course of

pinta. This new concept has been elaborated on by González Herrejón, Latapí and León y Blanco,[46] Gómez Farías, Briceño Rossi and Iriarte, Sáenz and his collaborators, Pardo-Castello and his associates, and Luis A. León. A summary of the important contributions to the knowledge of the clinical course of pinta may be found in the monograph of León y Blanco[49ff] and in the paper of Pardo-Castello and Ferrer,[60] and Holcomb.[40] The historic considerations of the knowledge of the early lesions of pinta are reviewed by Pequeño.[62] Excellent illustrations of Cuban cases are presented in the studies of Pardo-Castello and Ferrer and of Sáenz and his associates. Howard Fox's papers illustrate the Mexican and Colombian cases while Latapi and León y Blanco's[46] study profusely illustrates the early lesions of pinta.

The following is a condensed summary by León y Blanco of the course of pinta:

"Mal del pinto (pinta, carate) progresses through three distinct stages each showing different clinical, serological, and immunological characters.

"(*a*) The *primary stage* begins at the very moment of infection and lasts the period of time the lesion remains alone. Such period varies from individual to individual, being between 5 months and 1 year, or perhaps more. Clinically the primary or initial stage is characterized by the development of a papule at the point of infection, after an incubation time of 7 to 20 days. This papule gradually becomes an erythematosquamous patch, variable in outline and size within 30 to 50 days. During its long-lasting evolution it spreads slowly around the affected area, or other papules begin to appear peripherally, which in turn increase, and with similar erythematosquamous patches coalesce with the initial one.

"The appearance of these erythematosquamous lesions varies greatly from one patient to another, as well as in the same individual, according to the developmental stage of the ill condition. The types more frequently observed are the trichophytoid, psoriasiform, lichenoid, and large patches of variable morphology.

"(*b*) The *secondary stage* is characterized by skin rashes or papules, which rapidly change with diversely outlined erythematosquamous lesions and for which we have proposed the name 'pintids.' This stage is reached after 5 to 12 or more months have elapsed from the date of infection. The initial lesion keeps on evolving during the secondary stage and becomes indistinguishable from the pintids.

"(*c*) *Tertiary* or *dyschromic stage* shows acromic or pigmentary spots, erythema, follicular keratosis, keratoderma and superficial atrophoderma. Cuban, Colombian, and American investigators have reported aortitis and pathological disturbances of the heart sounds; Mexican authors have also reported vagosympathetic disturbances as well as lymph node swellings generalized to the superficial nodules."

The dyschromic phases of pinta are well described by Fox[26b] as follows:

"Blue pinto consisted of slaty-blue pigmentation which was present in 25 cases on certain favorite sites, such as the face, waistline and trochanteric region and constituted the most unique feature of the disease. It appeared either as shiny aggregated puncta or as diffuse patches and in some cases was widely disseminated. On the head and neck, the bluish patches occurred in order of frequency on the nose and cheeks, the chin and lower part of the forehead, the neck, the lips, the ears and the vermilion border of the lips.

"White pinto, representing the terminal stage of complete depigmentation, was the most disfiguring and resembled ordinary vitiligo except that it was

always associated with other characteristic changes of the skin. It was present in 23 cases and showed a predilection for bony prominences such as the knuckles, elbows, knees and ankles. Another favorite site was the flexor surface of the wrist.

"Partial depigmentation was observed in 30 cases, occurring most frequently in association with other pigmentary changes. It was usually diffuse and often occupied extensive areas such as the greater part of the back and extremities. In some cases it consisted of pin head lesions intermingled with brownish hyperpigmented or bluish puncta, forming reticulated areas of most bizarre pattern. A favorite site for this type was the flexor aspect of the upper extremities, especially the forearms.

"Brownish hyperpigmentation was observed at the border of the vitiligoid patches and as pea to bean sized cafe-au-lait spots on areas of partial depigmentation."

In addition to the cutaneous manifestations, pinta resembles syphilis in involving certain of the viscera, especially the heart and aorta. The cerebrospinal fluid changes have been cited above. Aortitis was reported by Thonnard-Neumann, Comacho Moya and Brewster[74] first; then by Pardo-Castello and by Sáenz and his collaborators. Pardo-Castello and Ferrer[60] found 20 cases (64.5% of 41 cases) with enlargement of the aorta and thickening of the aortic wall. The authors believed age was possibly a factor in some of the cases but high blood pressure was present in 8 cases, in 5 of which no aortic changes could be ascertained. Sáenz and his coworkers[68] observed cardiovascular lesions in 23.3% of their cases. They noted, incidentally, that keratosis of the palms and soles were frequent in the Cuban cases.[49cc]

Pinta thus represents another milestone in the efforts to evaluate the syphilis-like diseases. It is another example of the speed and the completeness with which modern investigative methods can organize from scattered beginnings the completely evaluated picture of a disease entity.[7c] With the discovery of an organism, morphologically indistinguishable from *Spirochæta pallida*, the laws of Koch have been fulfilled only a little less than in syphilis. But with this discovery of the treponemal cause of pinta, comes rationalization of effective therapy previously used empirically. With increased knowledge of the clinical aspects of the disease and the possible modes of its transmission, prophylaxis can be successfully employed. Credit is due to the indefatigable industry of the workers in our neighboring Latin American countries.

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